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SUBSCRIPTIONS: United States $12.00 a year; Canada $13.00; Foreign $16.00
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MAIL CHANGES OF ADDRESS AND SUBSCRIPTION ORDERS TO: The American Journal of Medicine, 466 Lexington Avenue, New York 17, N. Y. Changes of address must reach us one month in advance.

MANUSCRIPTS: All manuscripts should be typewritten double space and submitted to the Editorial Office of The American Journal of Medicine, 466 Lexington Avenue, New York 17, N. Y. The top should be indicated on the back of each photograph. Reference style: Hall, C. A. Erythrocyte dynamics in liver disease. Am. J. Med., 28: 541, 1960.

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REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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Vol. XXX MARCH 1961 No. 3

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Clinical Studies

The Clinical Diagnosis of Atrial Septal Defect in Children
JOHN R. EVANS, RICHARD D. ROWE AND JOHN D. KEITH 345

An analysis is made of the clinical, radiologic and electrocardiographic data in 186 cases of proved atrial septal defect to determine how securely it is possible to separate, on the basis of such examinations, ostium primum from ostium secundum anomalies, and to detect associated lesions or defects. The most reliable means for differentiating secundum from primum defects proved to be the electrocardiogram. The former usually showed a mean axis of the QRS complex lying between plus 60 degrees and minus 150 degrees and clockwise rotation of the frontal vector; the latter were distinguished by left axis deviation and counterclockwise rotation of the frontal vector. Complications of secundum defects included pulmonary hypertension, pulmonary stenosis, anomalous pulmonary venous drainage and mitral stenosis. In addition to mitral clefts, some primum defects were associated with tricuspid incompetence or common atrioventricular canal. When these various complications can be suspected and how far their presence can be established is discussed.

The Natural History of Ventricular Septal Defects in Infancy and Childhood. Based on Serial Cardiac Catheterization Studies
JOSHUA LYNFIELD, BENJAMIN M. GASUL, RENE ARCILLA AND LAWRENCE L. LUAN 357

The prevailing view, that patients with ventricular septal defects are prone to rapid development of irreversible pulmonary hypertension and pulmonary vascular disease, hence should be subjected to the risks of corrective surgery in infancy, is here challenged. Thirty-two such patients were studied by serial cardiac catheterization over a period of years. In the first two years of life there is a high incidence of pulmonary hypertension and increased pulmonary blood flow but, if not too high, the trend was found to be to lower values with increasing age. This may be due to the circumstance that the ventricular septal defect does not increase in size commensurately with normal growth of the heart, hence becomes relatively smaller with time. These and other interesting points brought out have implications for the roles of medical and surgical management in these anomalies.

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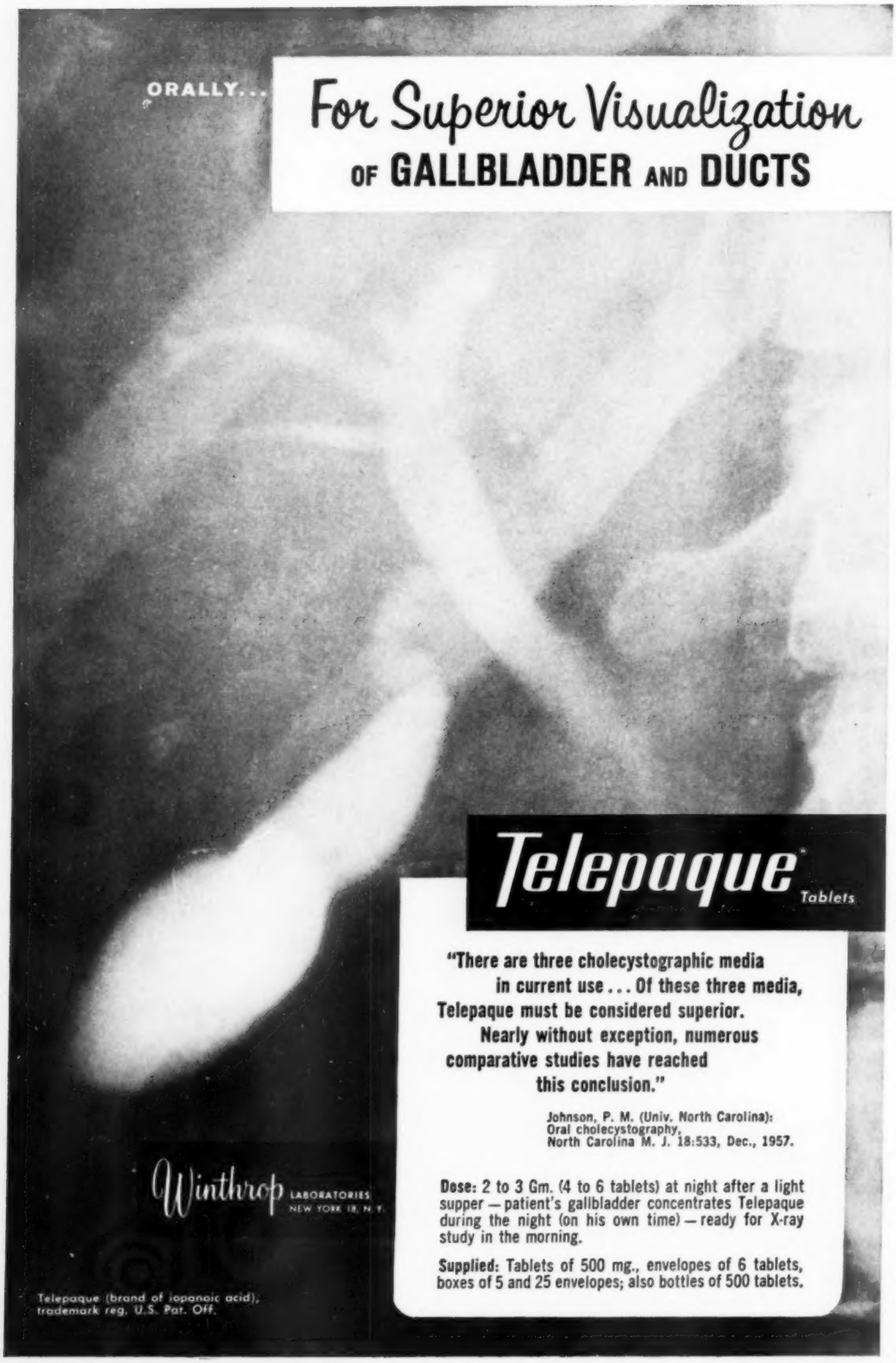
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Clinical and Hemodynamic Features of Advanced Rheumatic Mitral Regurgitation. Review of Sixty-Five Patients

LAMBERTO BENTIVOGLIO, JOSEPH URICCHIO AND HARRY GOLDBERG 372

This analysis of sixty-five cases of advanced mitral regurgitation reflects modern attitudes toward this valvular lesion, emphasizing much that has been appreciated only in recent years, largely through surgical experience. It is now realized that predominant mitral regurgitation is relatively benign only in the sense that a longer interval is apt to intervene between acquisition and congestive failure. The factors contributing to the development of failure are several, as pointed out herein. Assessment of the degree of regurgitation accompanying mitral stenosis remains difficult, even with the aid of modern hemodynamic studies.

Familial Cardiomyopathy . . . . E. J. BATTERSBY AND GEORGE G. GLENNER 382

Evans' concept of a familial form of cardiomegaly due to idiopathic involvement of the myocardium has been widely accepted but remains a nebulous and uncertain entity. The present report offers convincing documentation in the form of a sibship of which five members appear to have had a similar form of myocardial impairment of otherwise unexplainable etiology; at necropsy in two instances diffuse scarring of the myocardium was found, together with medial hypertrophy of small blood vessels and an excess of an unidentified polysaccharide in the myocardial fibers. All this would suggest that perhaps some unrecognized inborn error of metabolism, apparently particularly involving the myocardium, is responsible.

The Coronary Blood Flow as a Critical Determinant of Cardiac Performance and Cardiac Size

MARVIN BACANER, JOHN E. CONNOLLY AND DAVID BRUNS, WITH THE ASSISTANCE OF EDGAR STORLI AND JEROLD LOWENSTEIN 392

In this study varying degrees of cardiac failure were produced in the dog by graded constriction of the pulmonary artery, the resultant changes in hemodynamics particularly coronary blood flow were recorded, and the salutary effects noted of shunting of blood from the inferior vena cava to the lower abdominal aorta. Such shunting almost immediately improved coronary blood flow, cardiac performance and peripheral hemodynamics, in the face of continued pulmonary artery constriction of a degree theretofore completely incapacitating. In some animals the improvement continued even when the shunt was then discontinued. These observations seem to point up adequacy of coronary blood flow as the critical factor in determining cardiac performance and diastolic size, at least under the conditions of these acute experiments, a point argued at some length. They may also have clinical application; although institution of a venoarterial shunt, such as described, would be a formidable procedure in patients with myocardial infarction and shock, one such attempt was made.

Calcification of the Pulmonary Artery in Patent Ductus Arteriosus with Reversal of Blood Flow. Report of Four Cases

ALPHONSE E. TIMPANELLI AND ISRAEL STEINBERG 405

In four patients who had patent ductus arteriosus with reversal of flow, there was calcification of the wall of the pulmonary artery and/or its main branches. The authors suggest that this finding be

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*Pomeranze, J.: J. New York M. Coll. 1:32, 1959.

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sought in the conventional roentgenogram, since it strongly suggests the diagnosis of patent ductus with reversed shunt. The implications of reversal of shunt in patients with patent ductus are so important in respect to prognosis and management that this diagnostic criterion deserves attention.

Reviews

Syncope. Physiological Considerations and an Analysis of the Clinical Characteristics in 510 Patients . . . . . CAPT. HOWARD H. WAYNE 418

This discussion of syncope, here simply defined for purposes of classification as "temporary loss of consciousness," begins with a general consideration of the main types and causes of syncope: those due to cerebral ischemia, of generalized cardiovascular or localized arterial nature; those due to changes in the composition of the blood; and those resulting from intrinsic cerebral dysfunction. This is admittedly an artificial and overlapping separation of etiologies but it serves the purpose, particularly when the author characterizes the presyncopal, syncopal and postsyncopal periods of each variety. To illustrate the features and relative importance of each major type, Dr. Wayne draws upon an analysis of the case records of 510 patients with syncope. A number of interesting points are brought out.

Colchicine. Clinical Pharmacology in Acute Gouty Arthritis STANLEY L. WALLACE 439

Colchicine has been known for centuries as a specific agent in the treatment of acute gouty arthritis, yet its mechanism of action remains unexplained. This review collates the available information on colchicine (and certain analogs), its metabolic fate in man, and what little is known of its pharmacologic effects. Even when all this is put together, its mode of action in acute gouty arthritis remains speculative.

Combined Staff Clinic

The Effect of Mitral Commissurotomy on the Natural History of Rheumatic Heart Disease 449

Combined Staff Clinic (Columbia University College of Physicians and Surgeons).

The subject of this clinic is a currently worrisome one—the criteria for selection of patients for mitral commissurotomy, and the criteria for assessment of the results of surgery. The discussion is based on long-term observations (in contrast to the more usual short-term accounts) in 130 patients followed-up for an average period of forty-six months. Judged by clinical standards, 44 per cent were improved, 22 per cent were unchanged, 11 per cent were worse, 24 per cent were dead. In some cases, cardiac catheterization was performed before and after mitral commissurotomy, and on the whole the criteria emerging from these physiological measurements are comparable to those formed on clinical grounds. An important distinction to be made, if possible, is that between mechanical mitral block and myocardial insufficiency but there is, of course, overlapping and the morbid anatomy of the mitral valvulitis causing obstruction to flow of itself influences the natural and unnatural course of the disease. An honest and objective effort is made to arrive at firm criteria and evaluations but, for reasons discussed, no easy formula is yet available.

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Clinicopathologic Conference

Acute Renal Failure of Obscure Etiology 464

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

The Changing Pattern of Circulating Iodinated Amino Acids in a Case of Thyrotoxicosis . . . . . J. J. RUPP AND K. E. PASCHKIS 472

A significant observation; thyrotoxicosis characterized chiefly by circulating triiodothyronine (not, as customary, by circulating thyroxine) and, because of the greater potency of triiodothyronine, without increase in protein-bound iodine.

Reversal of Diurnal Rhythm in Excretion of Water and Salt in Primary Hyperaldosteronism

EDWARD J. LENNON, PHILIP P. RUETZ AND WILLIAM W. ENGSTROM 475

A report of unusual interest, of a hypertensive patient who first attracted attention because of reversed diurnal rhythm in the renal excretion of water and electrolytes. Penetrating studies disclosed the presence of primary hyperaldosteronism and of an unusually sensitive mechanism limiting expansion of body fluids. Each of these factors, their interactions, and their possible cause and effect relationship are informatively discussed.

Precipitating Antifibrinogen Antibody Appearing after Fibrinogen Infusions in a Patient with Congenital Afibrinogenemia

ANDRE DE VRIES, TUVIA ROSENBERG, SHAUL KOCHWA AND JOCHANAN H. BOSS 486

A well studied case of congenital afibrinogenemia exhibiting antibody formation to fibrinogen after replacement therapy.

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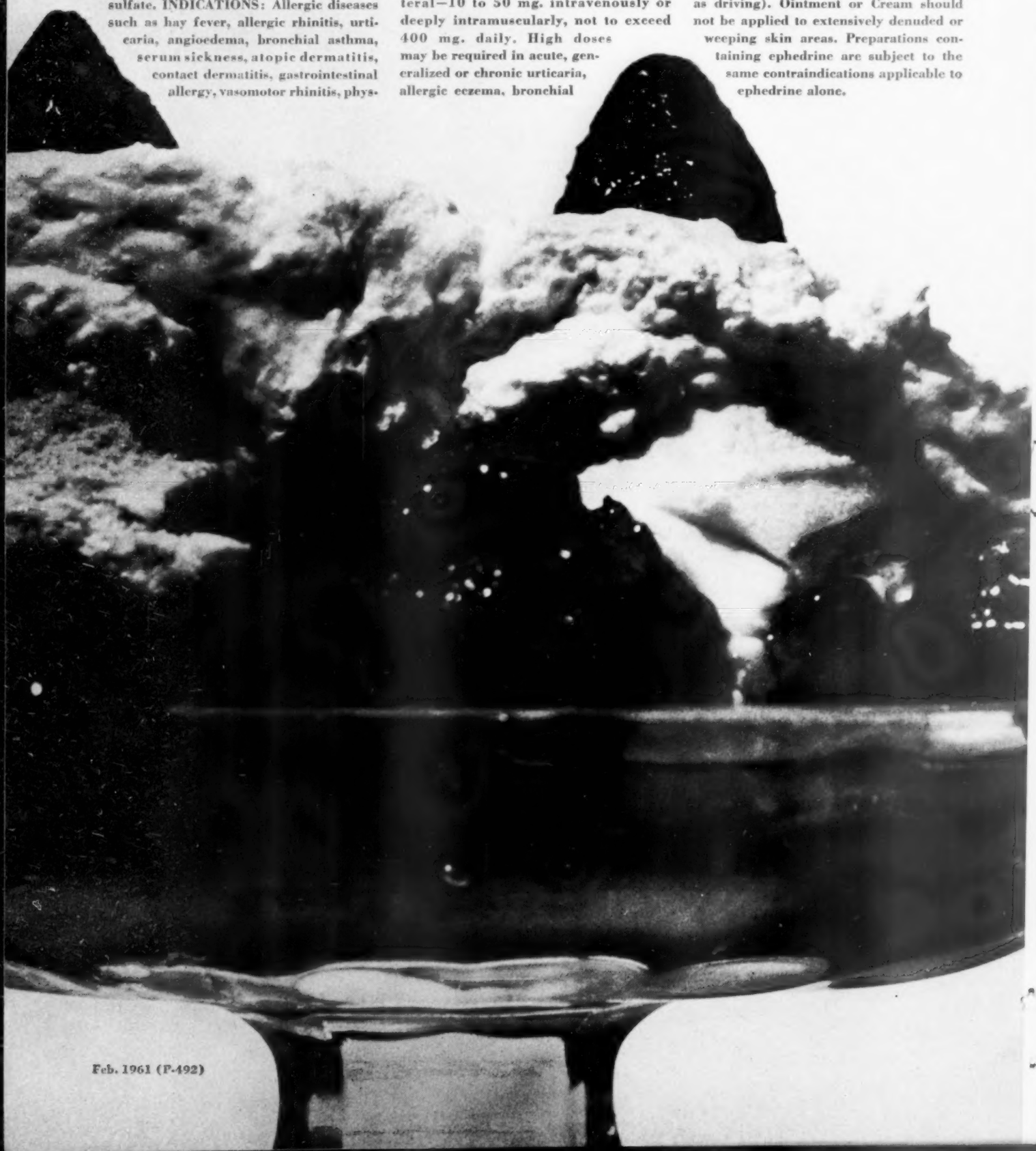

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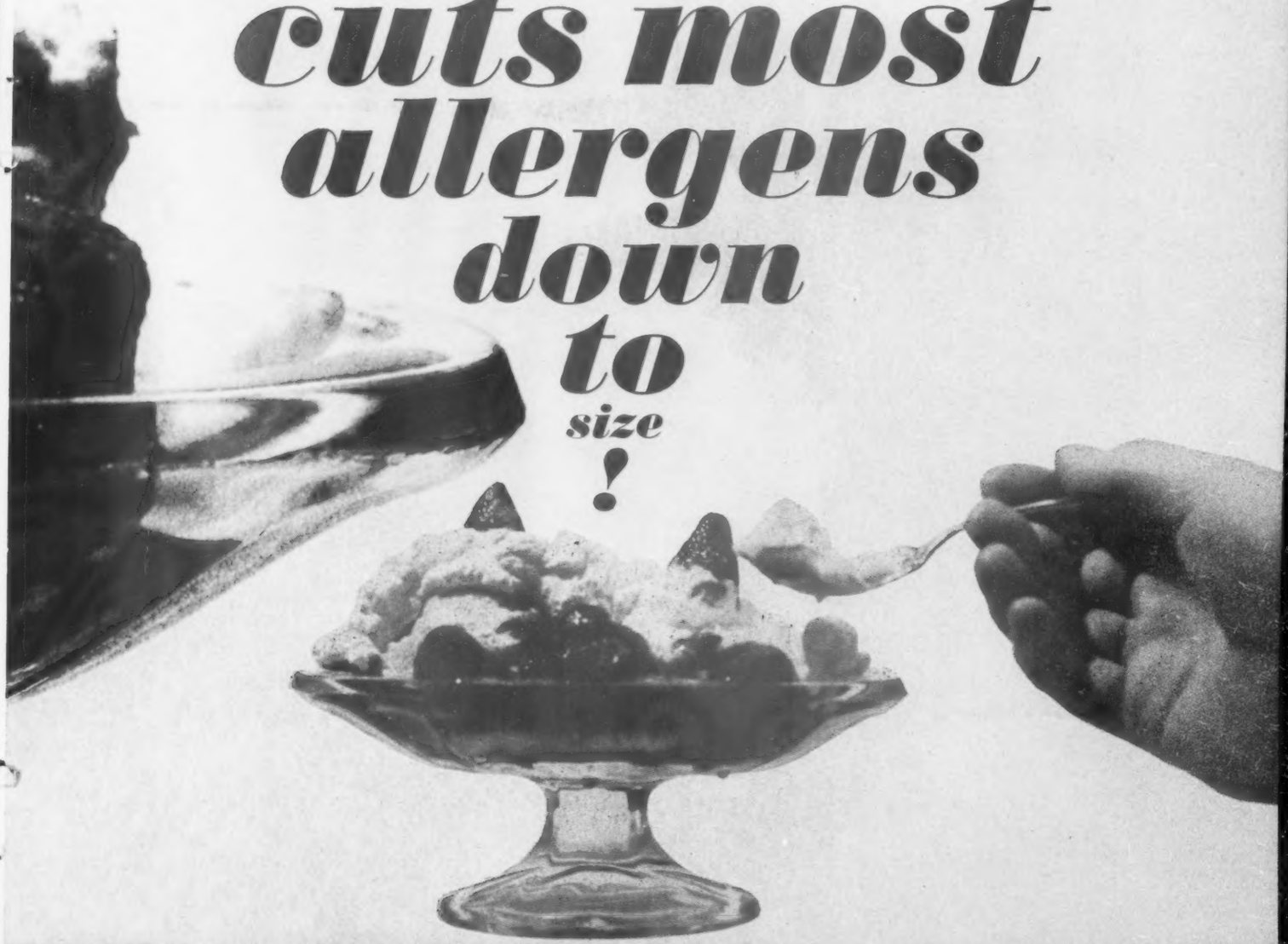

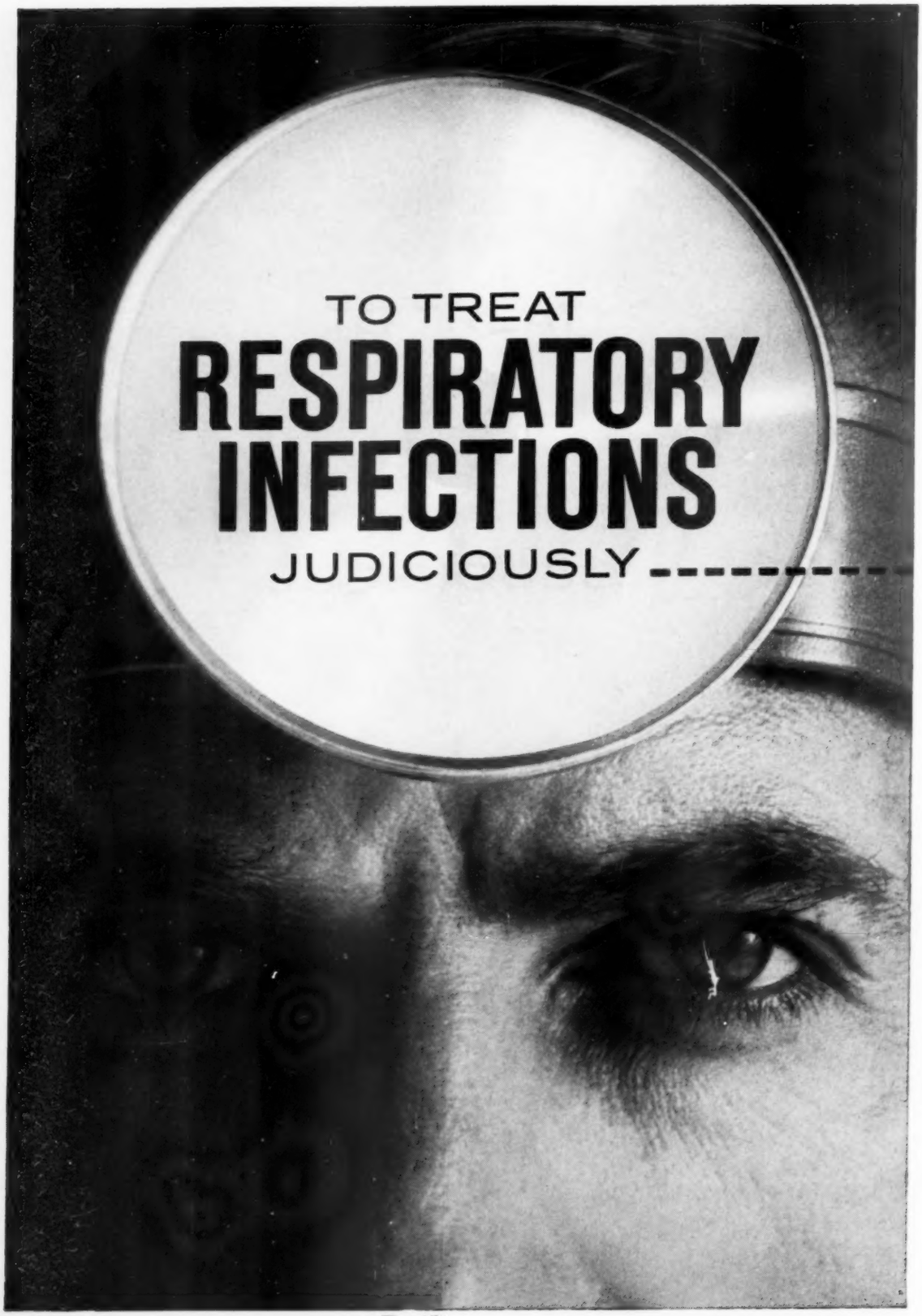
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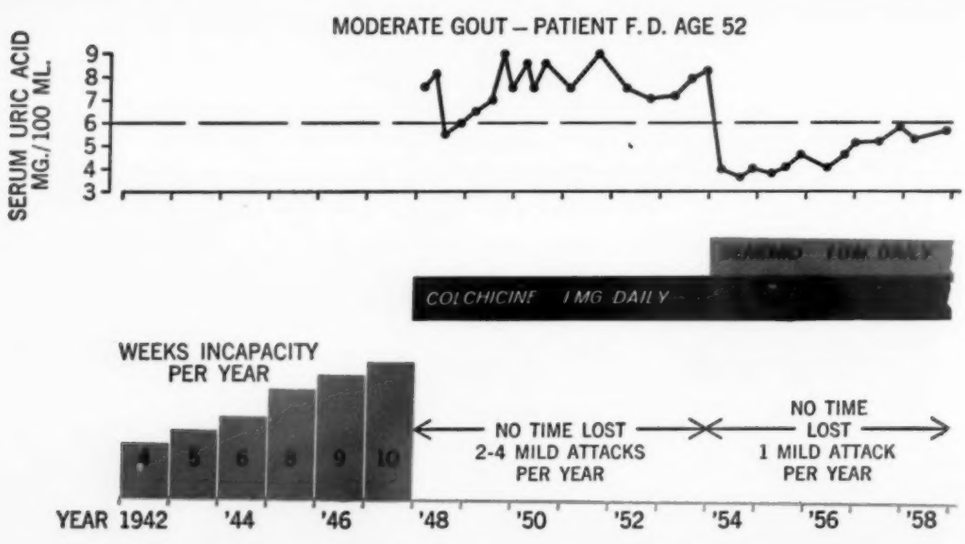

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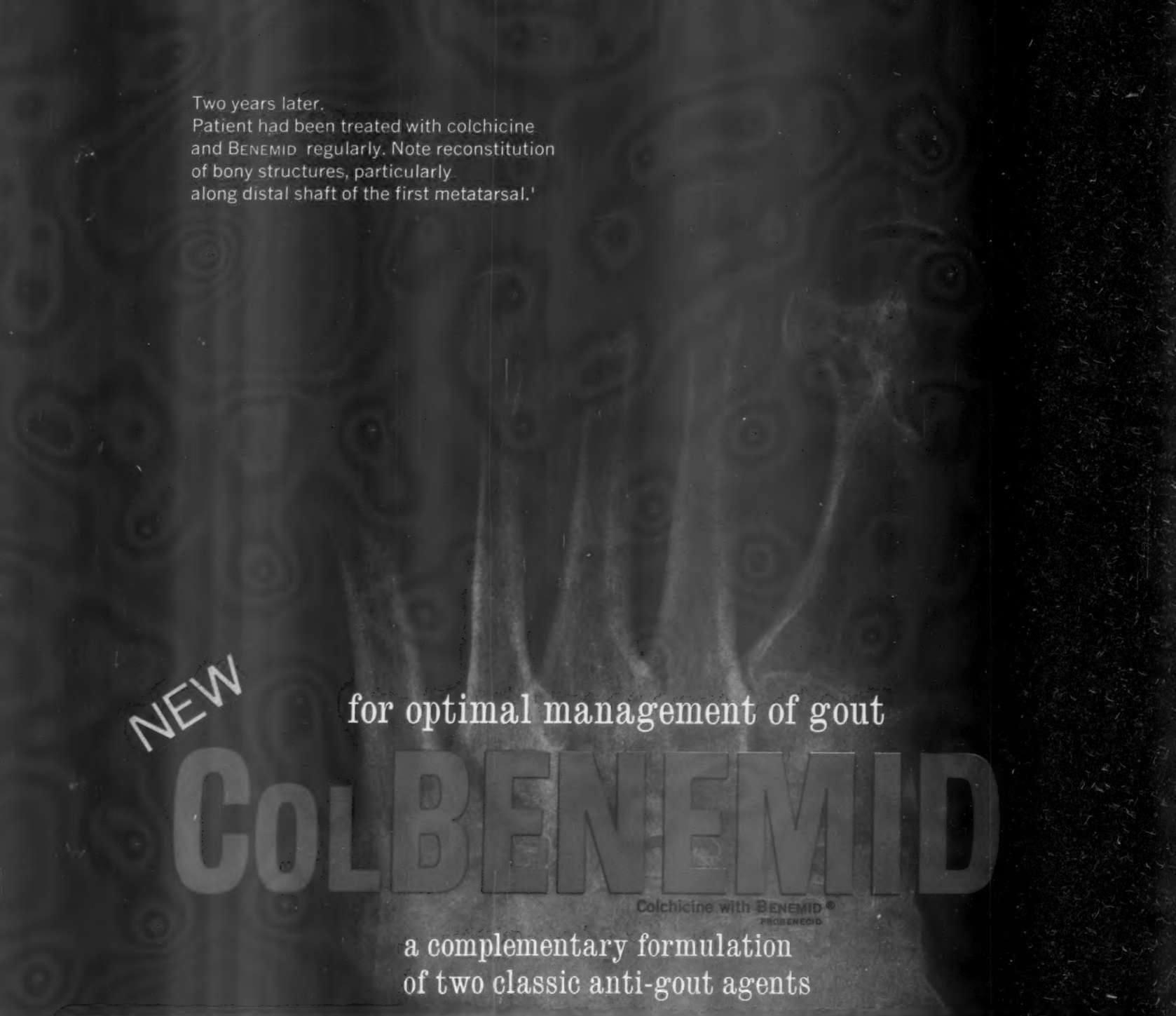
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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
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4. Bellet, S.: Amer. J. Cardiology 4:268, 1959.

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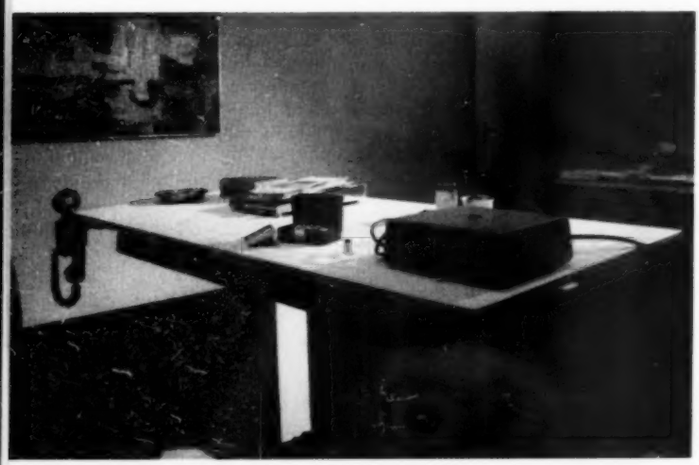
ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)



(In practical terms,

here's what Enduron's longer duration

means to you):

Dosage once a day, every day. Even in frank edema, once daily is all you need. Easy for patient to remember and stick to, easy for you to supervise.

No therapeutic gap between doses. Round the clock effectiveness. Your first dose provides good diuretic and hypotensive action that's sustained right up to the time next day's dose takes over.

Peak natruresis at 10 mg. level. Maximum sodium output occurs with each single 10 mg. dose. Natruresis remains well above control (i.e., undosed) level more than 24 hours. Larger single doses give no added effect, aren't needed.

Enhanced potassium-sparing effect. Enduron's single daily dose causes but a temporary single peak of potassium loss (compared to multiple daily peaks with multiple-dose thiazides). Basic ratio of sodium excretion versus potassium is enhanced, too. Potassium depletion is rarely seen.

ENDURON is a distinctive analogue of the thiazide family, created by Abbott, and available under no other trade name. Usual adult dose is only 2.5 to 10 mg. once daily; this low milligram dosage provides the security of a very safe therapeutic ratio. Supplied in 5 mg. (No. 6812) and 2.5 mg. (No. 6827) grooved tablets. Literature promptly supplied upon request to Abbott Laboratories, North Chicago, Ill.

BIBLIOGRAPHY 1. Ford, R. V., Clinical-Pharmacologic Investigation of Methyclothiazide, a New Oral Diuretic; Comparative Clinical Effects of Hydrochlorothiazide and Methyclothiazide, Current Therap. Res., 2:422-430, Sept., 1960. 2. Bryant, J. M., Schvartz, N., Fletcher, L., Jr., Fertig, H., Schwartz, M. S., McDermott, J. D., Quan, R., Clinical Studies of the Anti-hypertensive Effects of a New Benzothiadiazine Diuretic, submitted for publication.

ABBOTT

©1960, ABBOTT LABORATORIES 102026

in any rheumatic 'itis'

Schering

'hand-itis'

IT MAY BE EARLY RHEUMATOID ARTHRITIS

'shoulder-itis'

IT MAY BE CHRONIC BURSITIS

'neck-itis'

IT MAY BE MYOFIBROSITIS

'ankle-itis'

IT MAY BE EARLY OSTEOARTHRITIS

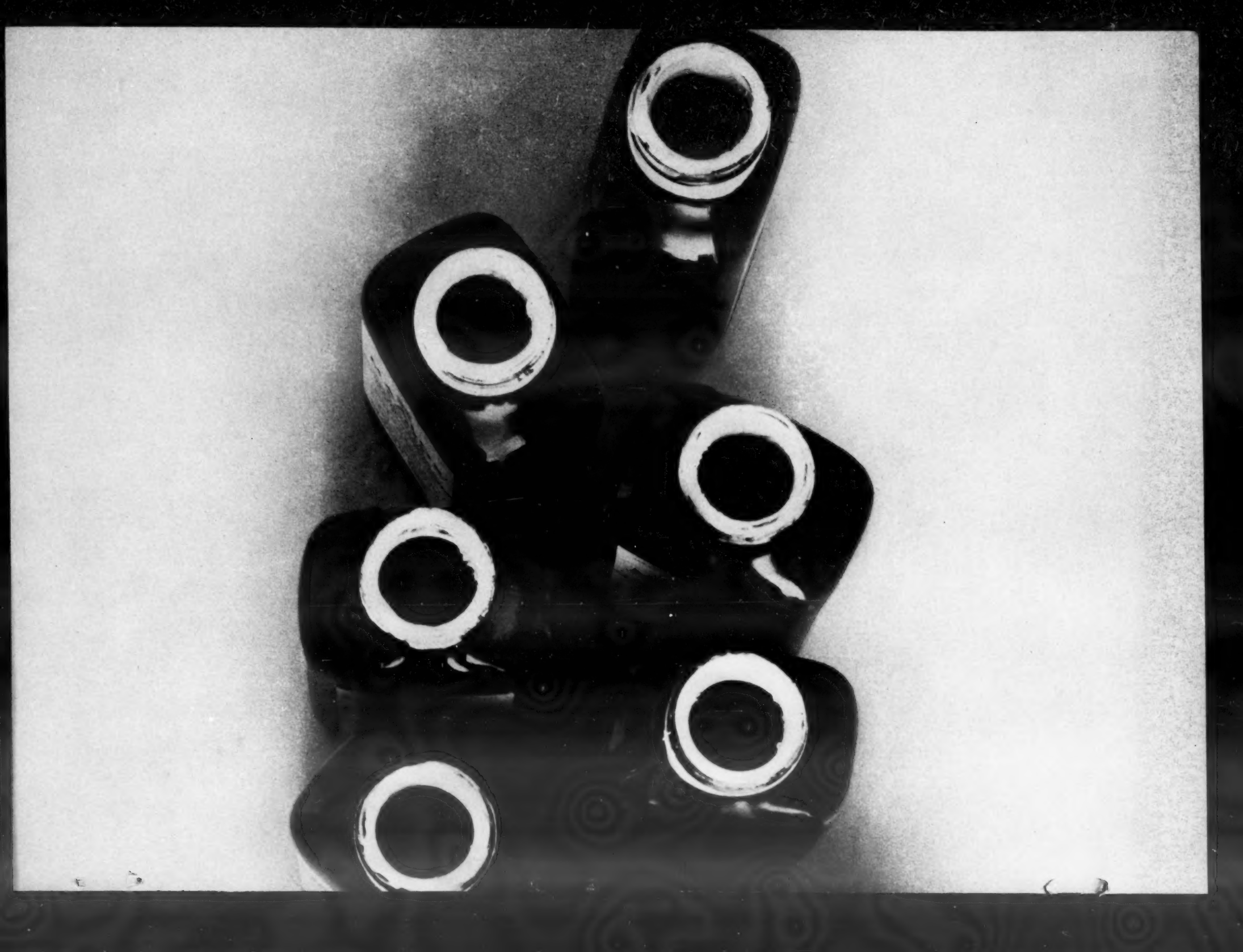
The favored corticoid-salicylate compound. For more effective and comprehensive, yet conservative, treatment than either steroids or salicylates alone... the outstanding anti-inflammatory effect of prednisone[1]... the supportive antirheumatic action of aspirin[2,3]... to bring rapid pain relief and quiet the inflammatory process. SIGMAGEN offers less likelihood of treatment-terminating side effects.[2] SIGMAGEN is available in bottles of 100 and 1000.

METICORTEN® (prednisone)	safer, reduced dosage	0.75 mg.
Acetylsalicylic acid	supportive anti-inflammatory-analgesic	325 mg.
Aluminum hydroxide	a buffer for better toleration	75 mg.
Ascorbic acid	anti-stress supplementation	20 mg.

References: 1. Cohen, A., et al.: J.A.M.A. 165:225, 1957. **2.** Spies, T. D., et al.: J.A.M.A. 159:645, 1955. **3.** Stecher, R. M.: Panel Discussion, Ohio M. J. 52:1037, 1956.

Remission-in any rheumatic 'itis' Sigmagen®

H-350



"wearability"

355 cc. (12 Ounces)
List No. 344
MAALOX®
RORER
(MAGNESIUM-ALUMINUM HYDROXIDE GEL)
ANTACID — DEMULCENT
NON-CONSTIPATING
A colloidal suspension of Magnesium and Aluminum Hydroxides useful for the relief of gastric hyperacidity.
Shake Well Before Using
Average adult dose: As antacid and protective, two to four teaspoonfuls may be given in water or milk twenty minutes after meals and at bedtime. Use as directed by your physician. Maalox should not be used in patients who are severely debilitated or suffering from kidney failure.
KEEP BOTTLE TIGHTLY CLOSED
KEEP FROM FREEZING
34772
WILLIAM H. RORER, Inc.
Pharmaceutical Chemists Philadelphia, Pa., U.S.A.

NO TASTE FATIGUE
EXCELLENT RESULTS
NO CONSTIPATION

the most widely prescribed and most wearable of all antacids

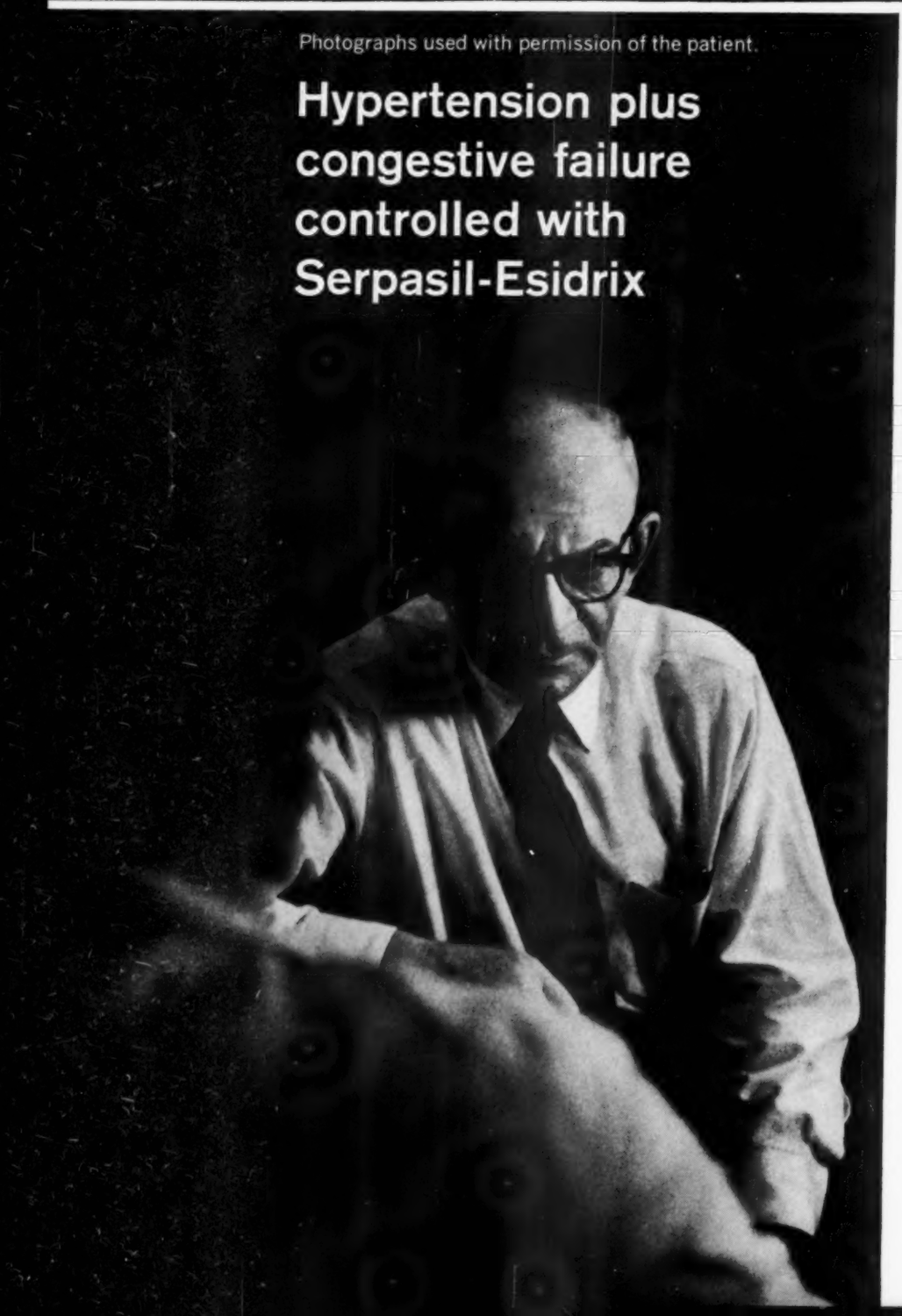
suspension tablets

Why combining Serpasil® with Esidrix® improves control of high blood pressure

Serpasil alone often relieves vasoconstriction and decreases arterial pressure in hypertensive patients. In many cases, however, excess fluid and sodium in the arteriolar environment can keep constricted blood vessels from dilating fully in response to antihypertensive therapy. By depleting excess fluid and sodium, Esidrix makes the vasculature more sensitive to other antihypertensive agents, thus enabling blood vessels to dilate to near-normal limits. When Serpasil is combined with

Photographs used with permission of the patient.

Hypertension plus congestive failure controlled with Serpasil-Esidrix



Mr. H. V., a 61-year-old retired pharmacist, suffers from hypertensive arteriosclerotic heart disease. In 1957 he was hospitalized after a myocardial infarction.

In addition to high blood pressure (range: 176/100 to 184/106 mm. Hg) the patient had associated congestive failure—with ankle edema and dyspnea.

Esidrix, peripheral resistance is reduced and blood pressure goes down – often to lower levels than can be achieved with single-drug therapy.

SUPPLIED: *Tablets* #2 (light orange), each containing 0.1 mg. Serpasil and 50 mg. of Esidrix; bottles of 100. *Tablets* #1 (light orange), each containing 0.1 mg. Serpasil and 25 mg. Esidrix; bottles of 100.

Complete information sent on request. s/2884 MK

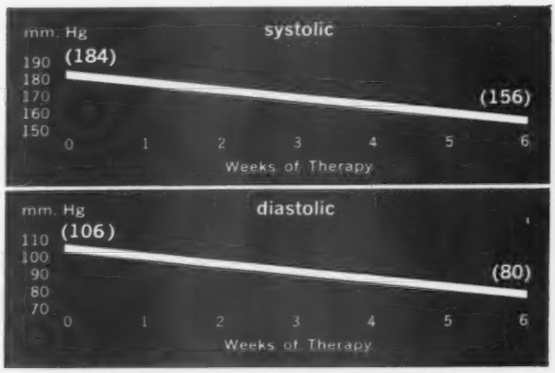
CIBA
SUMMIT·NEW JERSEY

Serpasil®-Esidrix®

(reserpine and hydrochlorothiazide CIBA)

Potentiated antihypertensive effect, single-tablet convenience

On April 4, 1959, Serpasil-Esidrix Combination Tablets #1 were added to the patient's existing regimen of digitalis and a low-salt diet. On Serpasil-Esidrix, blood pressure was lowered to a range of 156/80 to 166/84 mm. Hg. Examination on May 18, 1959, revealed no evidence of congestive failure. Neck veins were no longer distended, nor was there any ankle edema.



In the first six weeks of treatment with Serpasil-Esidrix, systolic and diastolic pressures decreased steadily. Blood pressure is now stabilized at a satisfactory level.

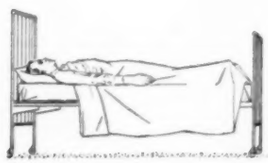
Mr. V. has had no side effects from Serpasil-Esidrix. His tolerance for exercise has increased; he can climb stairs without shortness of breath. Mr. V. gets around more easily and generally feels better.

a new agent to lyse thrombi

LYOVAC®

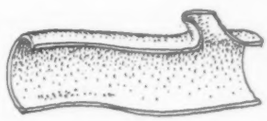
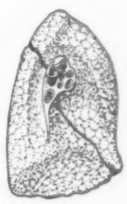
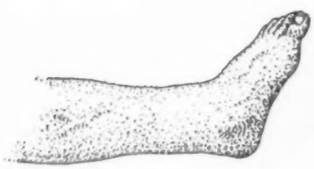
THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)

Results of therapy	Bed rest
Effect on intravascular thrombi	Clot may form permanent obstruction to blood flow. New clots may form.
Effect on pulmonary emboli	Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.
Effect on duration of illness and convalescence	 Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.
Frequency and severity of postphlebitic syndrome	Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.

In thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi*, THROMBOLYSIN makes possible
• lysis of formed clots • reduced mortality and morbidity, shortened hospitalization
• reduced incidence of postphlebitic complications
usually fewer severe untoward reactions, such as fever, chills, or malaise;
higher degree of safety; greater, more predictable potency.

Supply: **Each vial contains 50,000 MSD units.**
***Arterial thrombosis with the exception of cerebral or coronary thrombosis.**

Anticoagulant + Bed rest		THROMBOLYSIN + Anticoagulant + Bed rest	
	Anticoagulants cannot remove formed clot. However, they may help prevent its extension and may minimize formation of new clots.		Recently formed intravascular clots are usually lysed rapidly and the formation of new clots may be inhibited. Circulation is usually restored and maintained, with rapid symptomatic relief.
	The careful use of anticoagulants may reduce the occurrence of pulmonary emboli.		The incidence and severity of pulmonary emboli should be greatly reduced since THROMBOLYSIN may dissolve thrombi before they can become emboli.
	Thromboembolic illness and convalescence may be shortened.		A striking reduction is usually observed in the duration of hospital stay, bed rest, and convalescence.
	The incidence and severity of the postphlebitic syndrome may be reduced.		Postphlebitic complications may be prevented or minimized.

For additional information, write to Professional Services, Merck Sharp & Dohme, West Point, Pa.
MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.
THROMBOLYSIN IS A TRADEMARK OF MERCK & CO., INC.

"Crash diets" and "food substitutes" may reduce weight dramatically, but the greatest need is physician supervision for the remolding of indulgent eating habits.

Obedrin and the 60-10-70 Menu Plan provide supportive medication and a balanced eating plan *under your supervision.*

FORMULA: Tablets and Capsules

Semoxydrine HCl (Methamphetamine HCl)	5 mg.
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine Mononitrate	0.5 mg.
Riboflavin	1 mg.
Nicotinic Acid (Niacin)	5 mg.

THE S. E. MASSENGILL COMPANY

"sure... I used a crash diet... lost five pounds and now I've gained it all back!"

but to bring weight down and keep it down...

Obedrin®

and the 60-10-70 Menu Plan

Obedrin and the 60-10-70 Menu Plan will help you successfully treat patients who *must* reduce excess pounds and *maintain* optimum weight. Obedrin aids in curbing abnormal food cravings and facilitates establishment of correct eating habits.

Dosage can be individualized so appetite will be depressed at peak hunger periods. And Obedrin is the ideal support with its

- Methamphetamine — proved anorexigenic and mood-lifting effects
- Pentobarbital—balancing agent to guard against excitation
- Vitamins B_1 and B_2 plus niacin—effective diet supplementation
- Ascorbic Acid—aid for mobilization of tissue fluids

Calorie counting?

Not with the 60-10-70 Menu Plan; yet it assures balanced food intake with sufficient protein and roughage.

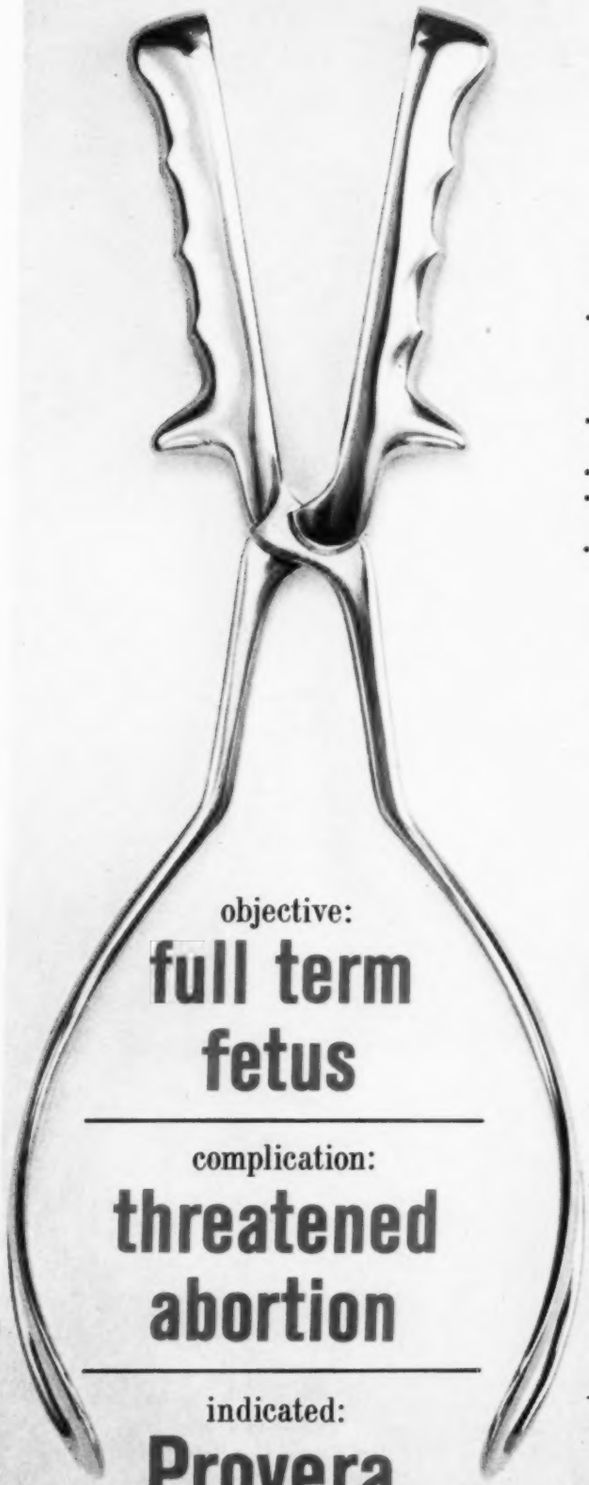
Write for

60-10-70 MENU PLANS, WEIGHT CHARTS AND SAMPLES OF OBEDRIN.

Supplied:

Tablets and capsules—bottles of 100, 500, and 1,000.

Bristol, Tennessee • New York • Kansas City • San Francisco



objective:

full term fetus

complication:

threatened abortion

indicated:

Provera

Upjohn

Here are five reasons why:

- Provera is the only commercially-available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized animals.
- It is four times as potent (by castrate assay) as any other progestational agent.
- No significant side effects have been encountered.
- It is available for both oral and parenteral administration
- Provera gives the economy of effective action from small doses.

Brief Basic Information

	● Oral Provera*	⟵ I.M. Depo-Provera**
Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only. 50 mg. per cc., in 1 cc. and 5 cc. vials.†

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

*TRADEMARK, REG. U.S. PAT. OFF. **TRADEMARK

Schering

for your patient with

hypertension

these benefits from

Naqua™

trichlormethiazide

often the only drug required for satisfactory reduction of blood pressure in both mild and moderate hypertension... commonly relieves headache, palpitation, etc.[1]... may further reduce blood pressure levels reached on previous regimens[2]... usually obviates need for potassium supplements... potentiates effect of some adjunctive antihypertensive agents, decreasing their dosage needs, thereby reducing their potential side effects... economically priced for special benefit of long-term patients. **Packaging:** NAQUA Tablets, 2 and 4 mg., scored, bottles of 100 and 1000. **References:** (1) Cohen, B. M.: Newer Saluretic Agents in the Therapy of Hypertension, paper presented at 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960. (2) Ford, R. V.: Am. J. Cardiol. **5**:407, 1960.

S-722

anticholinergic
KEEPS THE STOMACH FREE OF PAIN

tranquilizer
KEEPS THE MIND OFF THE STOMACH

Milpath acts quickly to suppress pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES:

Milpath-400 — Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

Milpath-200 — Yellow, coated tablets of 200 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath®

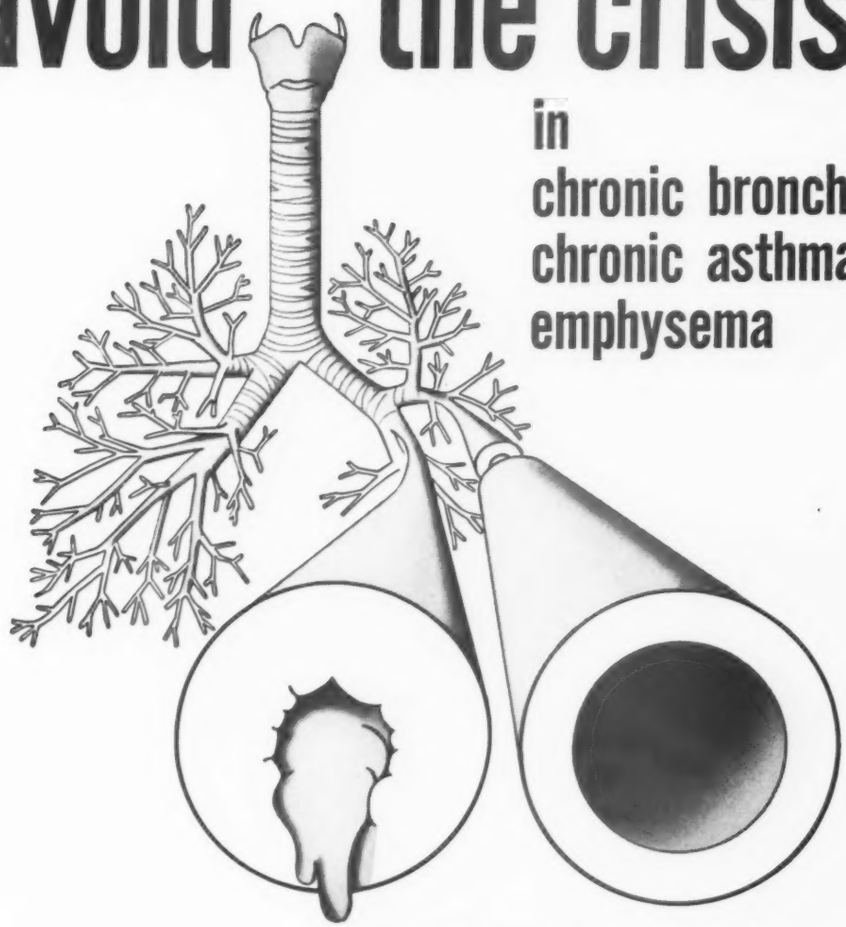
®Miltown + *anticholinergic*

WALLACE LABORATORIES *Cranbury, N. J.*

1278

to avoid the crisis

in chronic bronchitis chronic asthma emphysema



Choledyl provides uniformly effective bronchodilatation throughout long-term therapy. Taken regularly, Choledyl helps prevent severe flare-ups in patients with chronic respiratory disease (the aging in particular) by affording continuous relief from debilitating bronchospasm. Gastric irritation and other unwanted effects are rare.

CHOLEDYL®

THE CHOLINE SALT OF THEOPHYLLINE

brand of oxtriphylline

keeps the airways open

Supplied: 200 mg. tablets (yellow), bottles of 100. *Precautions:* Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. *Full dosage information, available on request, should be consulted before initiating therapy.*

WARNER CHILCOTT

MORRIS PLAINS, N.J.

makers of Tedral Gelusil Proloid Peritrate Mandelamine

6P12

another patient with hypertension?

indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES*

HYDRODIURIL® (HYDROCHLOROTHIAZIDE) with RESERPINE

HYDROPRES can be used:

- *alone* (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- *as basic therapy, adding other drugs if necessary* (Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- *as replacement therapy, in patients now treated with other drugs*

(In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25

25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50

50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

also available: **HYDROPRES-Ka-50**

50 mg. HydroDIURIL, 0.125 mg. reserpine, 572 mg. potassium chloride.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

*HYDROPRES, HYDROPRES-Ka, AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

to combat the three-pronged assault of urinary tract infections *— bacteriuria — tissue infection — discomfort*

UROBIOTIC®

COSA-TERRAMYCIN® — SULFONAMIDE — ANALGESIC

Only UROBIOTIC *contains:* OXYTETRACYCLINE (with glucosamine for enhanced absorption) — notable for its wide tissue distribution, high urinary concentration, excellent toleration and proven antibiotic effectiveness against even so troublesome an invader as *Pseudomonas;* SULFAMETHIZOLE — an unusually soluble, highly active sulfonamide; PHENYLAZO-DIAMINO-PYRIDINE — for effective local analgesia.

IN BRIEF

INGREDIENTS: Each Urobiotic capsule contains 125 mg. Terramycin® (oxytetracycline) with 125 mg. glucosamine HCl, 250 mg. sulfamethizole, and 50 mg. phenylazo-diamino-pyridine HCl.

INDICATIONS: Urobiotic is indicated in the treatment of a number of common genitourinary infections caused by susceptible organisms. It may also be used prophylactically before and after genitourinary or pelvic surgery, following instrumentation procedures, during the use of retention catheters, and in patients with conditions such as cord bladder or cystocele.

DOSAGE: In adults, a dose of 1 or 2 capsules four times daily is suggested, depending upon the severity and response of the infection. In children 60 to 100 lbs., the suggested average dose is 1 capsule four times daily; in children under 60 lbs., 1 capsule three times daily. Therapy should be continued for a minimum of 7 days or until bacteriologic cure is effected in acute urinary tract infections.

CONTRAINDICATIONS: Urobiotic may be contraindicated in patients with chronic glomerulonephritis, hepatitis, hepatic failure, uremia, and obstructive lesions of the urinary tract, and should not be used in patients sensitive to any of its components.

PRECAUTIONS: The use of broad-spectrum antibiotics may, in rare cases, result in an overgrowth of nonsusceptible organisms, such as monilia or staphylococci. Should such superinfection occur, therapy with Urobiotic should be discontinued and specific therapy instituted as shown by susceptibility testing. The use of sulfonamides may cause renal crystalluria or skin rash, as well as other toxic or sensitivity reactions. If any of these occur, discontinue use.

SUPPLIED: Urobiotic capsules, yellow-and-grey, bottles of 50.

Pfizer

More detailed professional information available on request.

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York Science for the world's well-being®

When the evidence indicates smooth muscle spasm,

good judgment can render it "null and void"
by a ruling in favor of
dependable autonomic sedation

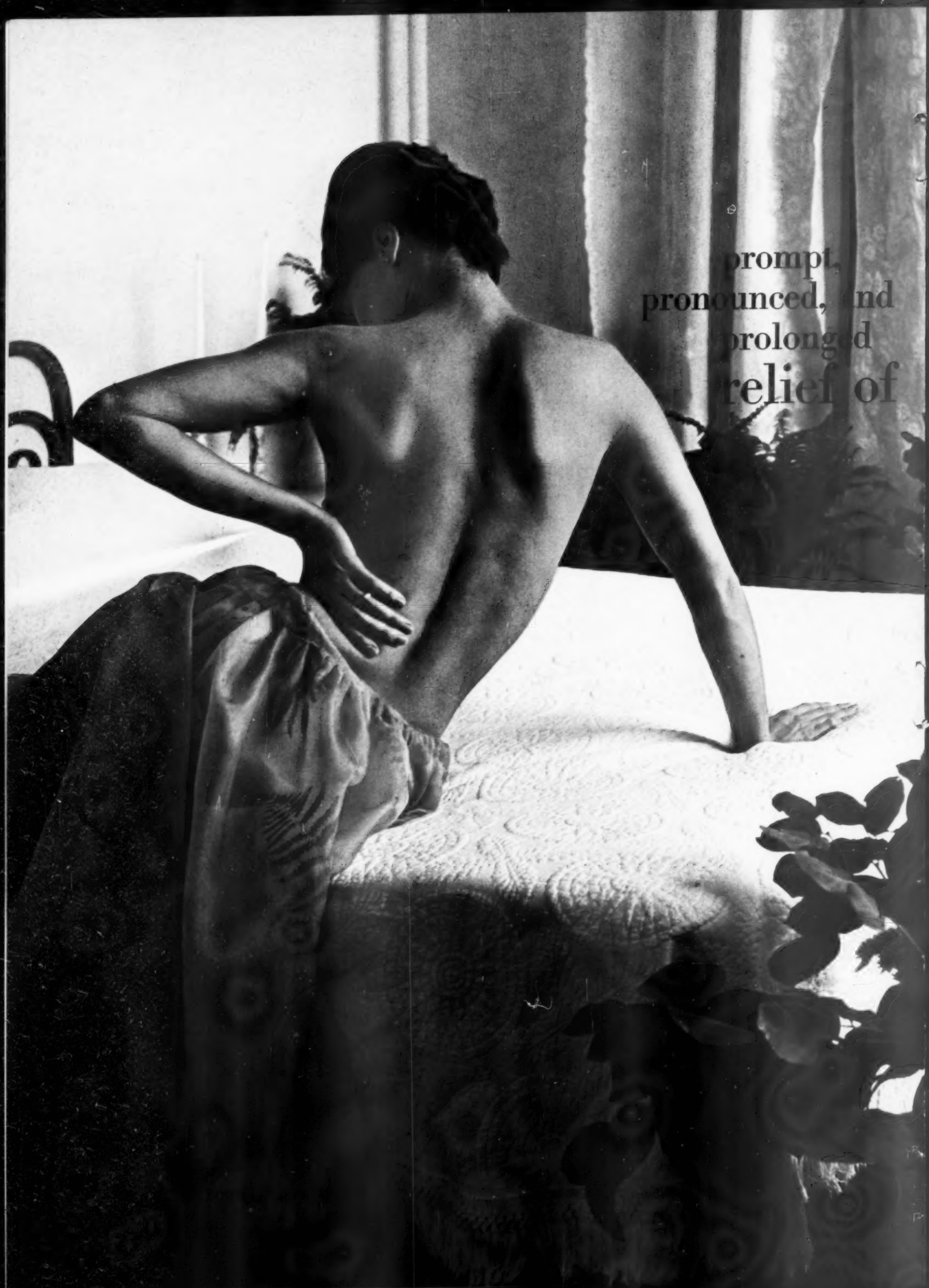
DONNATAL®

TABLETS • CAPSULES • ELIXIR • EXTENTABS

Natural belladonna alkaloids in optimal synergistic ratio, plus phenobarbital

A. H. ROBINS CO., INC., Richmond 20, Virginia

	In each Tablet, Capsule or tsp. (5 cc.) of Elixir	In each Extentab
Hyoscyamine sulfate	0.1037 mg.	0.3111 mg.
Atropine sulfate	0.0194 mg.	0.0582 mg.
Hyoscine hydrobromide	0.0065 mg.	0.0195 mg.
Phenobarbital	(¼ gr.) 16.2 mg.	(¾ gr.) 48.6 mg.


prompt,
pronounced, and
prolonged
relief of

painful skeletal muscle spasm

ROBAXIN®

Robins

INJECTABLE AND TABLETS Methocarbamol Robins U.S. Pat. No. 2770649

Relaxation – obtained *within minutes* with ROBAXIN Injectable.
– maintained *without drowsiness* with ROBAXIN Tablets.

Nine published studies show:

Beneficial results in 90% of cases of skeletal muscle spasm with ROBAXIN.

Clinical responses to ROBAXIN therapy, as reported by investigators:

"*marked*" in 26 out of 33 patients, moderate in 6...[1] "*pronounced*" in 37 out of 58 patients, moderate in 20...[2] "*good*" in 25 out of 38 patients, moderate in 6...[5] "*excellent*" in 14 out of 17 patients, moderate in 2...[6] "*significant*" in 27 out of 30 patients...[7] "*gratifying*" in 55 out of 60 patients...[8] "*effective*" in 32 out of 32 patients...[9] "*marked*" in 27 out of 46 patients, moderate in 6...[4] "*good*" in 57 out of 60 patients, moderate in 3.[10]

ROBAXIN exhibits "great freedom from undesired side reactions,"[3] does not produce "concomitant euphoria or partial anesthesia,"[10] and permits patients to retain concentration and awareness.[8]

For immediate relaxation of acute skeletal muscle spasm:

Robaxin® Injectable – **each ampul containing 1.0 Gm. of methocarbamol in 10 cc. of sterile solution.**

For initiating therapy or maintaining relaxation induced by ROBAXIN Injectable:

Robaxin® Tablets – **0.5 Gm. (white, scored) in bottles of 50 and 500.**

Also available: *When pain and spasm require concurrent analgesic and relaxant action:*

Robaxisal® Tablets – **Robaxin with Aspirin**

–and for skeletal muscle relaxation with more comprehensive analgesia:

Robaxisal®– PH – **Robaxin with Phenaphen®**

Literature available to physicians on request.

REFERENCES: 1. Carpenter, E. B.: Southern M.J. 51:627, 1958. **2.** Forsyth, H. F., J.A.M.A. 167:163, 1958. **3.** Hudgins, A. P.: Clin. Med. 6:2321, 1959. **4.** Grisolia, A., and Thomson, J. E. M.: Clin. Orthopaedics 13:299, 1959. **5.** Lewis, W. B.: California Med. 90:26, 1959. **6.** O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. **7.** Park, H. W.: J.A.M.A. 167:168, 1958. **8.** Plumb, C. S.: Journal-Lancet 78:531, 1958. **9.** Poppen, J. L., and Flanagan, M. E.: J.A.M.A. 171:298, 1959. **10.** Schaubel, H. J.: Orthopedics 1:274, 1959.

A. H. ROBINS CO., INC., Richmond 20, Virginia

Making today's medicines with integrity... seeking tomorrow's with persistence

HARVARD MEDICAL SCHOOL

Courses for Graduates

RECENT ADVANCES IN INTERNAL MEDICINE

June 5–10, 1961

By GEORGE W. THORN, M.D., and Associates at the Peter Bent Brigham Hospital

A course of instruction designed for internists of considerable clinical experience who wish to become acquainted with those recent developments in physiology, biochemistry and pathological chemistry which facilitate the understanding of the manifestations of disease and of its treatment. Lectures, seminars, and round-table discussions.

Tuition—$150

INTERNAL MEDICINE

June 1–30, 1961

By WALTER BAUER, M.D., and Associates at the Massachusetts General Hospital

A course providing an intensive survey of recent advances in internal medicine with emphasis on the correlation of clinical medicine with current concepts in basic biological sciences. The review includes recent progress in therapy, biochemical mechanisms of disease, medical genetics, advances in physiology, and the usefulness and interpretation of laboratory procedures. Instruction is carried out at an advanced level under the direction of senior physicians in each specialty area.

Tuition—$400

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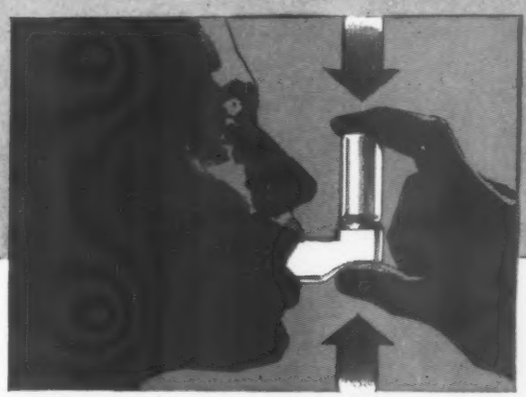

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1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

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Notable Success with VISTARIL...

in prepartum tension and anxiety		allays anxiety without impairing ability to cooperate during labor and delivery[1]	reduces narcotic requirements and incidence of narcotic-induced respiratory depression, helps control emesis[1,4]
in the cardiac or the hypertensive patient		allays anxiety without adverse influence on blood pressure[2]	helps correct certain functional arrhythmias, does not increase gastric secretion[2]
in problem drinkers		allays anxiety—makes patient more manageable[3]	produces no significant depression of blood pressure, pulse rate, or respiration. No liver involvement reported
in preoperative tension and anxiety		allays anxiety without depression of vital functions[4]	reduces incidence of narcotic-induced respiratory depression and hypotension, relaxes skeletal muscle, smooths recovery and helps control emesis[4]
in pediatrics		allays tension in agitated, hyperkinetic patients	avoids danger of liver damage or other untoward reactions

References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. Practice, Sept., 1960. 2. Salmons, J. A.: Dis. Chest 38:105, 1960. 3. Major, R. A.: GP 21:104, 1960. 4. Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

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IN BRIEF

Vistaril is hydroxyzine pamoate. The hydrochloride salt of hydroxyzine is used in the parenteral solution.

Vistaril acts rapidly in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear—whether occurring alone or complicating a physical illness. Used preoperatively and prepartum, Vistaril controls anxiety and fear, permits a substantial reduction in the amount of meperidine or other narcotic required for satisfactory analgesia, and helps prevent emesis. Vistaril's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with Vistaril, and it has a remarkable record of freedom from reactions.

INDICATIONS: Vistaril is clinically effective in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. *Recommended oral dosage:* In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially – adjust according to response. In cardiac arrhythmias: initial – 25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic—50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. *Recommended parenteral dosage:* In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Capsules* (hydroxyzine pamoate) – 25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate) – 25 mg. per 5 cc. teaspoonful. VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride) – 10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

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Acts directly on the inflammatory lesion **without** altering pituitary-adrenal function . . . **without** impairing immunity responses.[8,11]

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Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1,2,3]; gout[1,4,5]; acute superficial thrombophlebitis[6,7]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1-4]; severe forms of a variety of local inflammatory conditions[8,9,10].

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing. Full product information available on request.

Availability:
Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

References:
1. Graham, W.: Canad. M.A.J.: 82:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Kiem, I. M.: Arth. and Rheumat. 2:212, 1959. 3. O'Reilly, T. J.: J. Irish M.A. 46:106, 1960. 4. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. 98:31, 1959. 5. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 6. Stein, I. D.: Ann. N. Y. Acad. Sc. 86:307 (March 30) 1960. 7. Barczyk, W., and Röth, W.: Praxis 49:589, 1960. 8. Miller, J. M., et al.: Antibiotic Med. and Clin. Therap. 7:109, 1960. 9. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. 97:429, 1959. 10. Summary of individual case histories submitted to Geigy. 11. Domenjoz, R.: Ann. N. Y. Acad. Sc. 86:263, 1960. 12. Smyth, C. J.: Ann. N. Y. Acad. Sc. 86:292, 1960.

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Published papers† representing years of clinical experience in over 3,000 patients demonstrate the effectiveness and safety of Trimagill. Trimagill was used successfully in these cases primarily for acidification of the vaginal tract in treatment of vaginal infections. It was also used and is recommended as a non-absorbable agent following conization of the cervix to help eliminate postoperative sloughing, perineal odor, absorb secretion and maintain an acid pH.

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–Neustadt, D.H.: J.A.M.A. 170:1253 (July 11) 1959.

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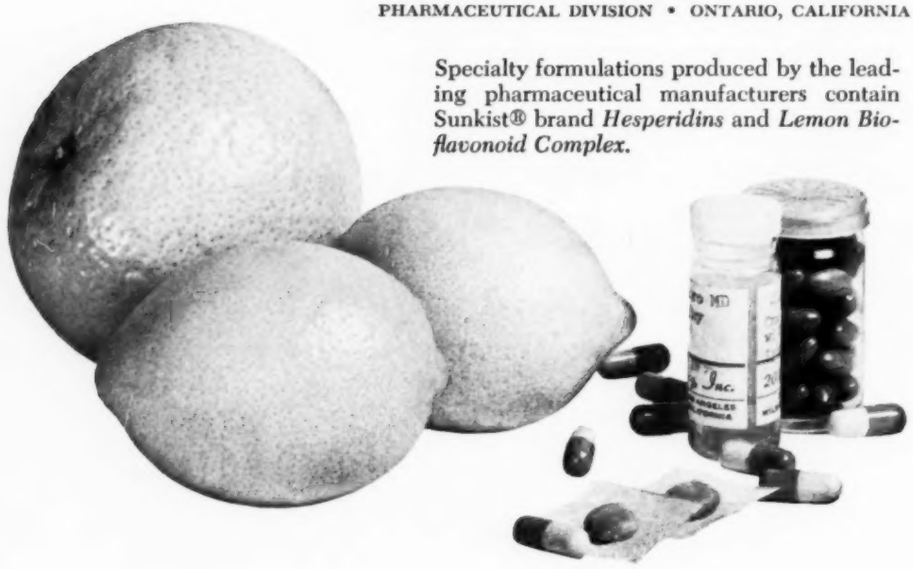

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1. A.M.A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, J. B. Lippincott Company, 1960, p. 363.
2. Friend, D. G., and Hamlin, J. T. III: in Modell, W.: Drugs of Choice 1960-1961, St. Louis, The C. V. Mosby Company, 1960, pp. 270-271.
3. Batterman, R. C., et al.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. 26:502-509 (Oct.) 1959.

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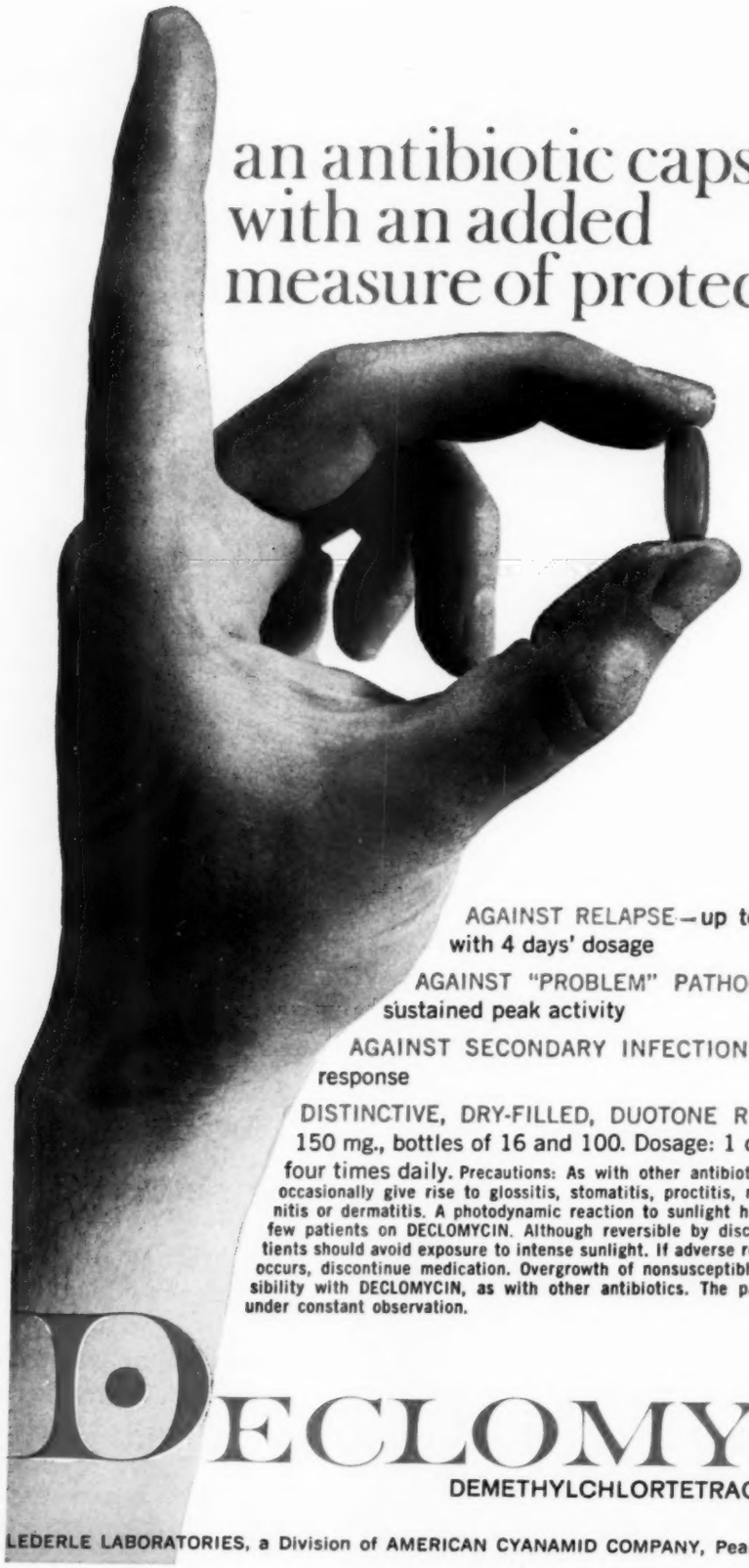

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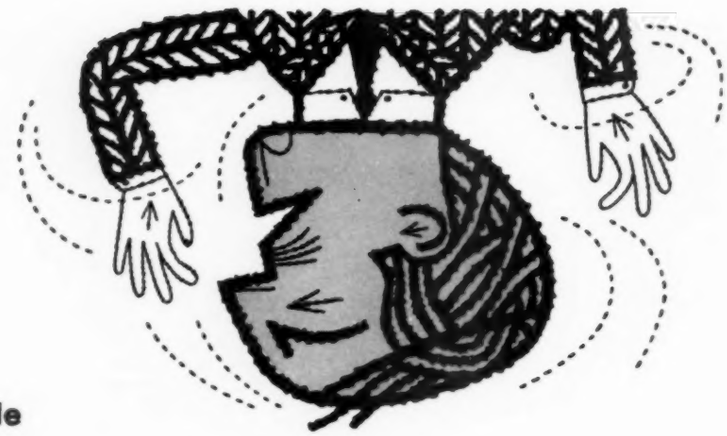

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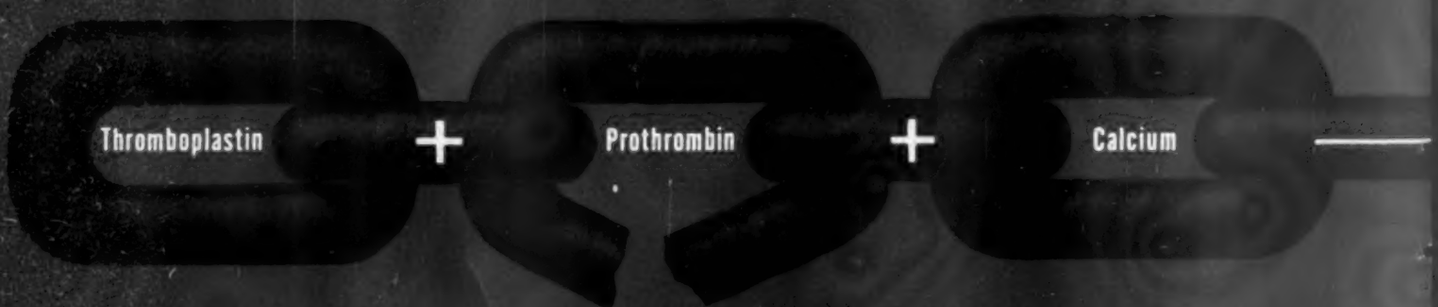

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*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.

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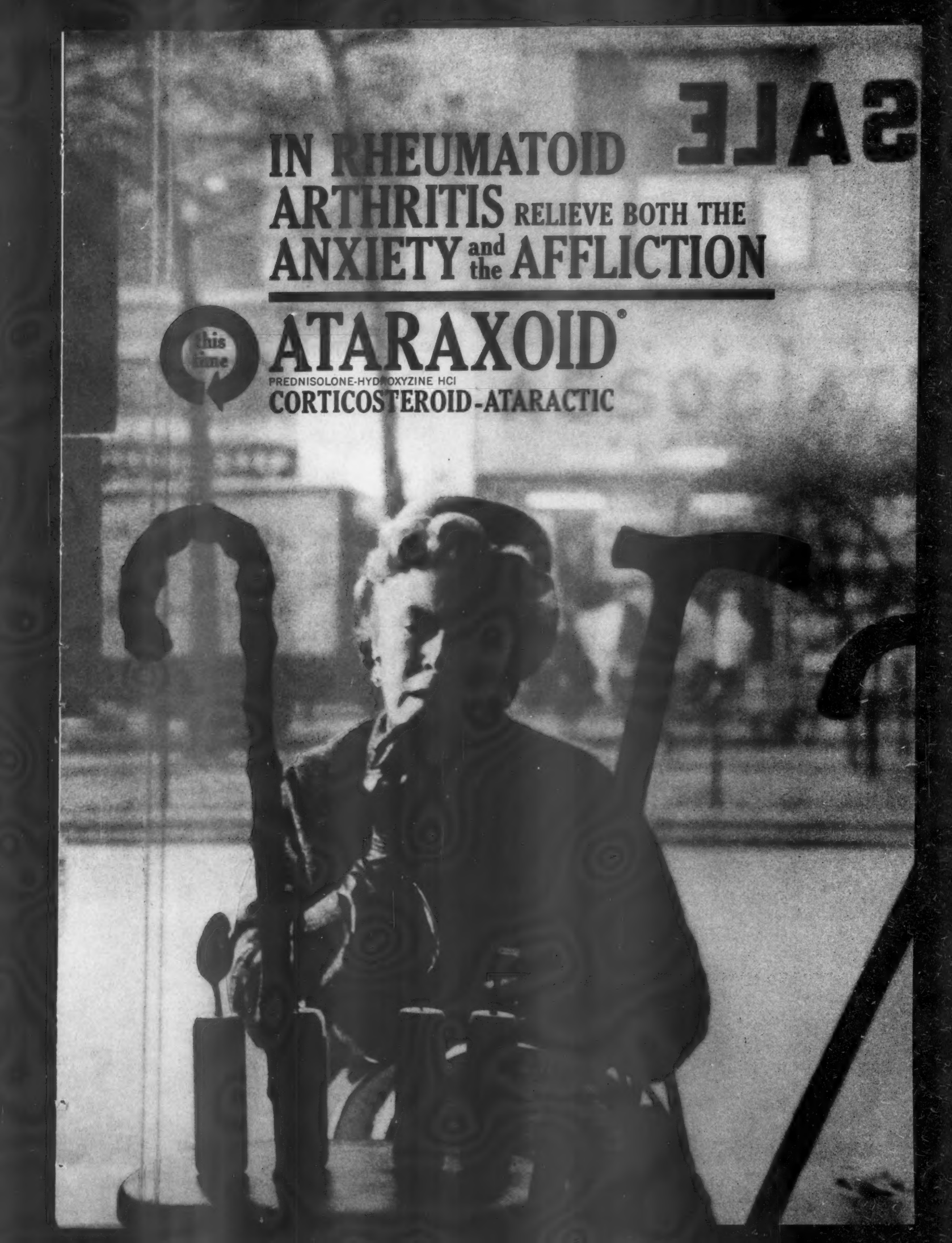
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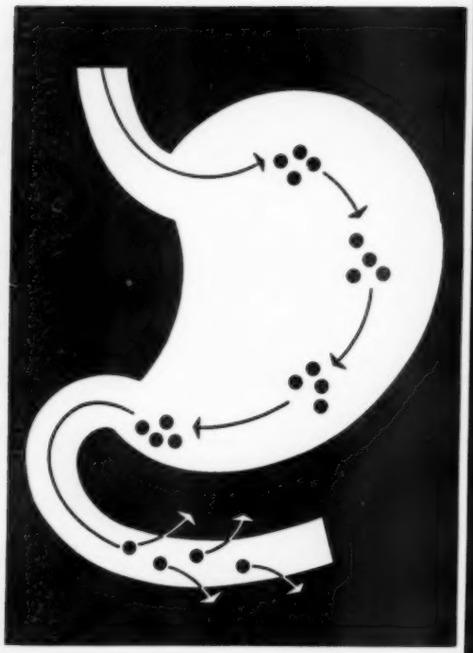

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1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:320, 1960.

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The American Journal of Medicine

VOL. XXX MARCH, 1961 No. 3

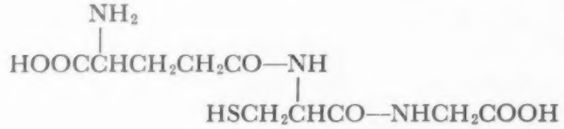
Editorial

Glutathione

Role in Conjugation in the Liver

RECENT studies indicate that glutathione participates in formation in the liver of a variety of conjugated organic compounds which are excreted in the bile and/or urine. Recognition of this central role of glutathione in providing a pathway by which many organic compounds are metabolized adds an important concept to our growing knowledge of this unusual tripeptide.

Glutathione was extracted from yeast in crude form, designated philothion, by De Rey-Pailhade in 1888 [*1*]. It was rediscovered in yeast, muscle and liver, and prepared in crystalline form, by F. Gowland Hopkins in 1921 [*2*]. The compound was identified as a tripeptide composed of glutamic acid, cysteine and glycine by Hopkins [*3*] and Kendall, McKenzie and Mason [*4*] in 1929. Synthesis of glutathione by Harington and Mead [*5*] in 1935 firmly established the structure as γ-glutamylcysteinylglycine:



Isherwood [*6*] has suggested that some of the properties of glutathione are best explained by the formation in solution of ring forms as a consequence of hydrogen bonding and related phenomena.

Glutathione is widely distributed in living cells but occurs in highest concentration in the liver [*7–10*]. It is found in a reduced form, GSH, and an oxidized form, GSSG, which are readily interconverted:

$$2\,GSH \rightleftharpoons GSSG + 2e + 2H^+$$

Only GSH is present in the liver, pancreas and kidney [*8*] and is maintained in the reduced form primarily by a specific enzyme, glutathione reductase, which is TPNH dependent:

$$TPNH + GSSG + H^+ \rightarrow TPN + 2\,GSH$$

The great reactivity of the SH group early suggested that glutathione may play a prime role in the hydrogen and electron transport systems of cellular oxidation and respiration, but studies of the kinetics of these reactions failed to establish the glutathione oxidation-reduction system as a major pathway. An important function for GSH has been found, however, in the protection of vital sulfhydryl-containing enzymes and other proteins by its reaction with potentially toxic substances such as peroxides and heavy metals. Glutathione also participates in transpeptidation and oxidative phosphorylation reactions and is a specific coenzyme in the oxidation of pyruvic aldehyde (methylglyoxal) to lactic acid. These and other reactions in which GSH is known to participate have recently been reviewed [*11–14*].

The newly recognized role of GSH, that of participation in the elaboration of conjugates with a number of organic compounds, is perhaps best exemplified by recent studies indicating the formation of a glutathione conjugate with bromsulphalein (phenoltetrabromphthalein di-

sulfonate, sulfobromophthalein). For a long time it was considered that BSP was excreted unaltered into the bile. However, in 1950 Brauer, Krebs and Pessotti [*15*] found that gradient elution of BSP in bile from an alumina column yielded several distinct peaks, all with identical absorption spectrums [*16*]. One of these peaks, representing a minority of the total BSP, was identical with the injected BSP, the others represented unidentified derivatives. Subsequently, Meltzer, Wheeler and Cranston [*17*], Combes [*18*], and Grodsky, Carbone and Fanska [*19*], achieved paper chromatographic separation of the BSP derivatives.

The study by Combes [*18*] of an isolated BSP derivative subjected to hydrochloric acid hydrolysis revealed the presence of glycine and glutamic acid. The precise nature of the conjugation became apparent when Javitt, Wheeler, Baker and Ramos [*20*], using S^{35}-glutathione and alkaline hydrolysis, demonstrated that all the conjugates present in canine bile contained cysteine which was bound to BSP via a thioether linkage. One of the conjugates, when isolated, was found to contain cysteine, glycine and glutamic acid, and to be identical in several respects with a synthetically prepared conjugate of BSP and glutathione (BSP-GSH).* Combes and Stakelum [*21*] also have identified a conjugate in rat bile as BSP-GSH. Grodsky, Carbone and Fanska [*22*], working chiefly with human bile, have identified cysteine, but were unable to determine if the glycine and glutamic acid found after hydrolysis derived from BSP conjugates or other constituents. Therefore, some uncertainty still exists as to whether the conjugates present in human bile are BSP-glutathione and/or BSP-cysteine.

In addition to BSP-GSH, BSP-cysteinylglycine conjugates [*23*] have been identified in canine bile. The excretion of these latter conjugates is associated with a marked increase in free glutamic acid in the bile, suggesting that BSP-cysteinylglycine is derived from BSP-GSH by transfer (hydrolysis) of the γ-glutamyl radical. A transferase catalyzing enzymatic transfer of the γ-glutamyl radical from GSH has been identified [*24*]. The marked rise in glutamic acid and glycine of human bile in association with the excretion of BSP conjugates [*25*] suggests that a similar phenomenon may occur in man.

The role, if any, of conjugation with glutathione in affecting the rate and extent of hepatic uptake, storage or biliary excretion of BSP has not been defined. Such studies would provide valuable information in assessing the meaning of increased plasma retention of BSP in liver disease.

The *in vitro* reaction between GSH and BSP [*23*] is comparable to the reactions reported with other halogenated organic compounds. Dickens [*26*] found that at pH 7.4 and at 37.5°C. the reaction between GSH and iodoacetate was half complete in ten minutes. Bromacetate was slightly less reactive, chloracetate participated slowly, fluoracetate not at all. The reaction is apparently dependent on the ease with which the halogen is split by the GS^- attack upon the reactive carbon. In each instance the same thioether derivative ($GSCH_2COOH$) is obtained. The ease with which these reaction take place *in vitro* under physiologic conditions of temperature and pH suggests that they may occur non-enzymatically. Bray, Thorpe and Vallance [*27*] studied the liberation of chloride ions from organic chloro compounds by tissue extracts and concluded that the liberation of chloride ions in the presence of liver extract takes place mainly as a non-enzymatic reaction between chloro compounds and SH compounds. However, the possibility of enzyme participation, perhaps of the dehalogenase type described by Heppel and Porterfield [*28*], was not ruled out.

These observations raise the possibility that some halogenated compounds other than BSP, when gaining access to cells rich in GSH, as in the liver, may enter into similar reactions to form thioether derivatives. A number of halogenated compounds are in common use as therapeutic agents and occasionally are hepatotoxic—chlorpromazine and chlorpropamide, for example. Iodine-containing compounds, both endogenous (thyroid hormone) and exogenous (contrast media), might also come under consideration in this connection.

Further evidence for glutathione conjugation can be found in the studies of mercapturic acid formation. Many organic compounds are excreted in the urine conjugated via a thioether linkage to cysteine with acetylation of the free amino group. These —C—SCH_2-$CHNHCOCH_3COOH$ derivatives isolated from urine have been classified as mercapturic acids.

* Since bromine is liberated [*23*] in the formation of the *in vitro* conjugate, it would be more accurately termed a phenoltribromphthalein disulfonate S-glutathione conjugate.

A comprehensive review of the numerous compounds studied has recently appeared [*29*]. Conjugation may proceed via substitution of a halogen or nitro group attached to a carbon, but may also occur with displacement of hydrogen from a reactive carbon. Mercapturic acids have been recognized as conjugates for many years but evidence for their derivation from glutathione conjugates formed in the liver has recently received new impetus. Stekol [*30*] found that administration of S-parabrombenzylcysteine and S-parabrombenzylglutathione to rats resulted in excretion of the same mercapturic acid. More recently, Bray and Franklin [*31*] reported that incubation of S-parachlorbenzylglutathione with liver slices yielded S-parachlorbenzylcysteine. Binet and Wellers [*32*] noted that administration of brombenzene resulted in a significant reduction in liver GSH content. Barnes and James [*33*] have also shown a similar reduction in the GSH content of the liver with 3:4 dichloronitrobenzene, 3:4:5 trichlorobenzene and benzylchloride. More direct evidence for the participation of GSH has been presented in the studies of Booth, Boyland and Sims [*34*]. They found that naphthalene, which is excreted as a mercapturic acid [*35*], forms a glutathione conjugate when incubated with rat liver homogenate. Furthermore, the naphthalene-GSH conjugate is hydrolyzed to a cysteine derivative on incubation with kidney homogenate and is then acetylated by liver slices or kidney homogenate. It would thus appear that the mercapturic acids found in the urine can be traced to glutathione-linked precursors in the liver.

Conjugation, which includes the synthesis of ethereal sulfates, glucuronides, mercapturic acids, amino acid conjugates and acetylated amines, is one of the hepatic mechanisms for metabolizing or disposing of a variety of compounds. The derivatives are frequently more water-soluble (polar) and less lipid-soluble (nonpolar) than the parent compound and therefore have less tendency to penetrate cell barriers [*36*]. The formation of the aqueous-soluble steroid and bilirubin glucuronides from their lipid-soluble precursors illustrates this mechanism. Conjugation may also affect the distribution and excretion of compounds in that the conjugates may become more available to an enzymatic transfer system, or undergo a change in pKa with altered ratio of dissociated and undissociated molecules. Although the exact mechanisms are ill defined, the net effect in most instances is to "detoxify" and enhance the removal of various compounds from the body.

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Clinical Studies

The Clinical Diagnosis of Atrial Septal Defect in Children*

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Toronto, Canada

A DIAGNOSIS of atrial septal defect can usually be made with confidence on the basis of the characteristic clinical findings [*1–5*]. These findings, however, may vary with the site of the defect and the presence of associated lesions. The present study reviews the clinical features of 186 children with atrial septal defect proved at surgery or necropsy, to determine whether or not physical, radiologic and electrocardiographic examination permit recognition of complicating lesions or defects in atypical sites.

MATERIAL

The patients ranged in age from one week to sixteen years. All were studied in the cardiac department of the Hospital for Sick Children, Toronto, where the history, physical examination and fluoroscopy were recorded. A complete electrocardiogram with six or more precordial leads was performed on all but two patients who had standard leads taken only. Criteria for the diagnosis of atrial and ventricular hypertrophy were those of Keith, Rowe and Vlad [*6*]. A vector loop in the frontal plane was drawn from the electrocardiogram in each case.

Arterial oxygen saturation was measured by ear oximetry in eighty-three patients both at rest and with exertion. Right heart catheterization was performed in 166 patients. Cardiogreen dye dilution studies were recorded at the ear with the Paul oximeter [*7*] in selected patients at cardiac catheterization.

Anatomic data were obtained at surgery in 134 patients and at necropsy in fifty-two. All but eight of the surgical patients were operated on at the Hospital for Sick Children, Toronto.

OBSERVATIONS

The patients were divided into two main groups according to the position of the atrial septal defect. All lesions remote from the atrioventricular valves were classified as *ostium secundum* defects. Low defects, lying immediately above the atrioventricular valves and often associated with a cleft in one or both valves, were considered to be *ostium primum* defects. When the primum defect was continuous with a deficiency in the membranous ventricular septum the syndrome was labelled *common atrioventricular canal.*

OSTIUM SECUNDUM DEFECTS

Ostium secundum defects were found in 136 children as an isolated lesion or in combination with other abnormalities. (Table I.) The majority were central in position but some were located near the entrance of the superior or inferior vena cava and one was posterior with the

TABLE I
INCIDENCE OF ASSOCIATED ABNORMALITIES IN 136 PATIENTS WITH OSTIUM SECUNDUM DEFECTS OF THE ATRIAL SEPTUM

Type of Lesion	No. of Patients
Isolated (five with pulmonary hypertension)	96
With pulmonary stenosis	13
With partial anomalous pulmonary venous drainage	10
With mitral stenosis	2
With rheumatic mitral incompetence	1
With ventricular septal defect	14
Total	136

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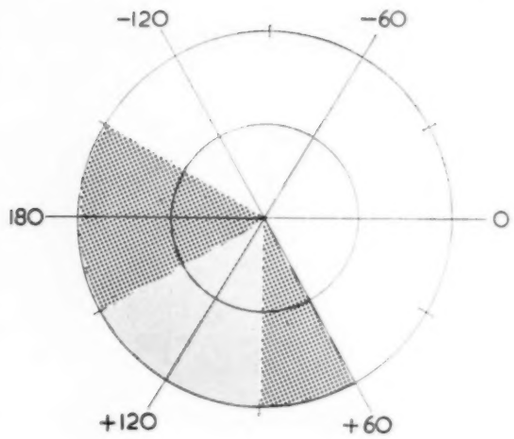


MEAN AXIS	NO. OF PATIENTS
+60° to +90°	9
+90° to +150°	72
+150° to −150°	8
Indeterminate	7

FIG. 1. Mean frontal axis of the QRS complex in ninety-six patients with ostium secundum defects of the atrial septum showing range of plus 60 to minus 150 degrees with peak incidence between plus 90 and plus 150. In seven patients the mean axis was indeterminate.

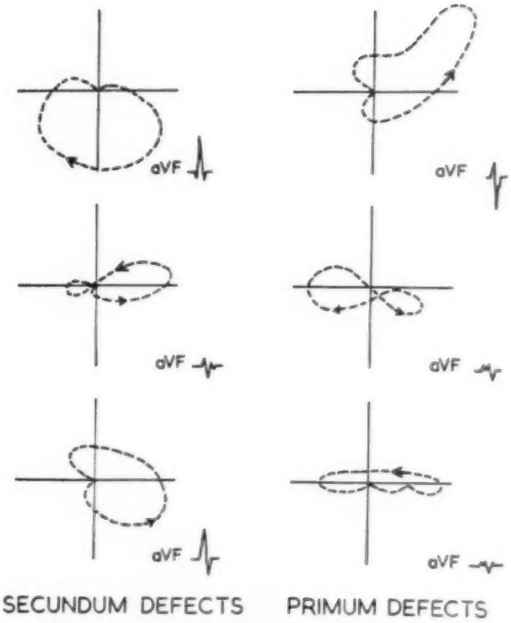


FIG. 2. Frontal vector of the QRS complex computed from the electrocardiogram of six patients showing clockwise loop usually seen with secundum defects and counterclockwise loop above the horizontal plane typical of ostium primum defects. Vectors with a figure-of-eight pattern or flat loop closely applied to the horizontal axis may be seen with either secundum or primum defects. The configuration of the QRS complex in lead aVF is shown alongside the vector loop.

right pulmonary veins at its margin. No consistent method was found for identifying the site of the lesion before operation. Although the embryologic origin may be different for secundum defects in various sites, from the standpoint of diagnosis and surgical correction it is advantageous to consider them all as one group.

Isolated Ostium Secundum Defects. Of ninety-six patients with isolated ostium secundum atrial septal defects, five had significant pulmonary hypertension and will be discussed separately. The clinical features of the remaining ninety-one patients followed a relatively uniform pattern.

Fatigue was the most common symptom but serious cardiac disability was rare. One-third of the patients were asymptomatic. Cyanosis was not encountered. Three patients had mild congestive failure which cleared quickly with digitalis therapy. The right atrial wall was thick in one and biopsy demonstrated endocardial fibroelastosis.

On physical examination splitting of the second heart sound was recognized in every patient and the pulmonary component was always of normal or slightly increased intensity. The width of splitting often varied with respiration, particularly in patients with smaller defects, but in no instance did the two components become synchronous on expiration to give the impression of a single second sound. The systolic murmur in the pulmonary area was accompanied by a thrill in two patients and in both cases this was described as faint. A soft mid-diastolic murmur was frequently heard at the lower left sternal border and, less commonly, a presystolic murmur was present. A dominant A wave, exceeding the V wave by 3 cm. or more, was never observed in the jugular venous pulse.

The heart was usually enlarged on radiologic examination but in no case did the cardiothoracic ratio exceed 0.65. The left atrium appeared slightly enlarged in four of eighty-six patients in whom this was assessed. The pulmonary vascular markings were considered normal in five patients with small defects, but in the remainder the hilar vessels were prominent and usually pulsatile.

The electrocardiogram showed some variant of the "incomplete right bundle branch block" pattern in all but two patients in whom an Rs complex was present in the right chest leads.

TABLE II

CLINICAL, HAEMODYNAMIC AND ANATOMIC FINDINGS IN FIVE PATIENTS WITH ISOLATED OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT IN WHOM PULMONARY HYPERTENSION WAS PRESENT

Patient and Age (yr.)	Cyanosis on Effort	Congestive Heart Failure	Cardiothoracic Ratio	Catheterization Findings			Anatomy of Atrial Septal Defect	
				Pulmonary Artery Pressure (mm. Hg)	Pulmonary : Systemic Blood Flow	Arterial O_2 Saturation (%)	Site	Area (sq. cm.)
A. S., 1¾	+	+	0.70	75/50	1.2:1	93	Central	1.5
G. M., 2	+	+	0.69	55/0*	3:1	90	Near inferior vena cava	6.0
L. B., 6	0	+	0.70	60/25	3:1	102	Central	9.0
P. A., 7	0	0	0.69	55/15	2:1	...	Central	7.5
S. W., 8	0	+	0.75	80/35	3.5:1	86	Central	12.0

* Right ventricular pressure (pulmonary artery not entered; no pulmonary stenosis at necropsy).

The height of the R wave in lead V_1 was greater than 16 mm. in four cases. The mean axis of the QRS complex lay between plus 60 and minus 150 degrees in all cases in which it could be readily measured, and in over three-fourths of the patients it fell between plus 90 and plus 150 degrees. (Fig. 1.) The frontal vector, computed from the electrocardiogram, was inscribed in a clockwise direction in each case. In seven patients the mean axis was indeterminate; in one the frontal vector was counterclockwise, and in the other six it formed a flat loop or "figure-of-eight" pattern closely applied to the horizontal axis. Examples of the clockwise figure-of-eight and counterclockwise frontal vectors are illustrated in Figure 2 with the electrocardiographic pattern of lead aVF alongside.

Cardiac catheterization was performed in eighty-three of the patients in this group. Two features warrant comment. A dominant A wave exceeding V by more than 3 mm. Hg was never seen in the pressure pulse of either the right or the left atrium. The mean pressure gradient across the atrial septum was always 2.5 mm. Hg or less.

Pulmonary Hypertension. Pulmonary hypertension with a pulmonary artery pressure greater than 50 mm. Hg was present in five of the ninety-six patients with isolated secundum atrial septal defect. (Table II.) The clinical features of this group were different. All had significant cardiac symptoms and two had cyanosis with effort. On examination the intensity of pulmonary valve closure was noticeably increased and usually palpable. A dominant A wave was observed twice in the jugular venous pulse. The heart size tended to be larger, and in all patients the cardiothoracic ratio exceeded 0.65. In the electrocardiogram, the height of R in lead V_1 was greater than 16 mm. in every case.

The incidence of pulmonary hypertension was higher when atrial septal defect was complicated by a second lesion such as a separate ventricular septal defect or partial anomalous pulmonary venous drainage (*vide infra*).

Pulmonary Stenosis and Atrial Septal Defect with Left-to-Right Shunt. The association of pulmonary stenosis with atrial septal defect and persistent left-to-right shunt was encountered in thirteen patients. (Table III.) An atrial septal defect of the secundum type was present in each case but in one patient there was, in addition, a small ostium primum defect without deformity of the atrioventricular valves.

Cyanosis on exertion confirmed by oximetry was noted in five patients. A systolic thrill was felt in the pulmonary area in all but one patient. Closure of the pulmonary valve was abnormal and suggested an anatomic defect of the valve in nine patients: in seven it was delayed and soft, and in two it was delayed and snapping in character. A mid-diastolic

TABLE III

CLINICAL AND HAEMODYNAMIC DATA IN RELATION TO FINDINGS AT OPERATION IN THIRTEEN PATIENTS WITH PULMONARY STENOSIS AND ATRIAL SEPTAL DEFECT WITH PERSISTENT LEFT-TO-RIGHT SHUNT

Patient and Age (yr.)	Cyanosis with Exertion*	Pulmonary Valve Closure	Cardiothoracic Ratio	Electrocardiogram R/S V_1 (mm.)	Systolic Gradient Right Ventricular—Pulmonary Artery (mm. Hg)	Pulmonary Systemic Flow Ratio	Operative Findings		Systolic Gradient Postoperative Right Ventricular–Pulmonary Artery (mm. Hg)
							Area of Atrial Septal Defect (sq. cm.)	Pulmonic Stenosis Diameter (cm.)	
E. M., 15	0	Not recorded	0.57	18/1	75	2.7:1	9.0	Moderate	...
L. K., 7	+	Not recorded	0.53	13/1	70	2.7:1	10.5	Moderate	...
N. E., 4	0	Soft and delayed	0.51	22/4	65	1.6:1	4.5	0.5	...
D. M., 2	+	Soft and delayed	0.73	17/11	77	1.7:1	6.0	0.7	...
S. S., 4	0	Snapping, delayed	0.53	16/0	(85)†	1.6:1	9.0	0.7	...
R. B., 6	0	Soft and delayed	0.56	25/0	52	2.9:1	4.0	0.8	...
K. M., 10	+	Soft and delayed	0.50	20/1	50	1.3:1	6.0	‡	25
M. P., 11	+	Soft and delayed	0.48	33/5	50	2.3:1	12.0	‡	25
L. H., 11	0	Delayed	0.43	12/2	50	3.5:1	6.0	...	...
D. V., 7	+	Soft and delayed	0.53	26/2	40	2.1:1	4.5	...	5
M. B., 9	0	Delayed	0.50	11/3	40	2.3:1	4.0	‡	25
B. S., 10	0	Delayed	0.48	13/3	35	2.3:1	9.0	...	10
K. V., 9	0	Snapping, delayed	0.54	16/0	20	2.1:1	8.0	‡	15

* Confirmed by oximetry.
† Right ventricular pressure (pulmonary artery not entered).
‡ Systolic thrill over base of pulmonary artery after atrial septal defect closed.

murmur was heard in one patient only. A dominant A wave was observed in the jugular venous pulse of six patients.

The heart size tended to be small with the exception of one patient (D. M.) in whom regurgitation through a deformed tricuspid valve was associated with marked dilation of the right atrium. The cardiothoracic ratio was 0.55 or less in ten of the thirteen patients. In four patients the left pulmonary artery was dilated and its origin unusually high, as seen in pulmonary stenosis with intact septums. The pulmonary vascular markings were increased and pulsatile in five patients but appeared normal in the others.

The electrocardiogram in these patients did not differ from those with isolated atrial septal defect with respect to P-R interval, p waves or QRS axis. The R wave in V_1, however, was 16 mm. or more in ten of the patients. The configuration of V_1 was R or notched Rs in eight of the thirteen patients and rsR′(s) in the remainder.

The systolic pressure gradient across the pulmonary valve ranged from 20 to 77 mm. Hg at cardiac catheterization. The right ventricular pressure pulse was symmetrical with a pointed peak in keeping with valvular stenosis. In every case a small or moderate left-to-right shunt was present at atrial level but no right-to-left shunt was detected under resting conditions.

Moderate pulmonary stenosis was relieved

TABLE IV

CLINICAL, HAEMODYNAMIC AND ANATOMIC FINDINGS IN TEN PATIENTS WITH ATRIAL SEPTAL DEFECT AND PARTIAL ANOMALOUS PULMONARY VENOUS DRAINAGE TO THE RIGHT ATRIUM OR SUPERIOR VENA CAVA

Patient and Age (yr.)	Cyanosis with Exertion	Right Ventricular Pressure (mm. Hg)	Anomalous Veins Detected at Catheterization	Gradient of Mean Pressure from Left Atrium–Right Atrium (mm. Hg)	Site of Drainage of Anomalous Pulmonary Veins*	Atrial Septal Defect	
						Area (sq. cm.)	Site
D. W., 5	0	35/5	+	4	Right atrium (2) Superior vena cava (1)	2	Near superior vena cava
J. L., 9	0	45/0	+	...	Right atrium (2) Superior vena cava (1)	2	Near superior vena cava
N. H., 13	0	25/0	+	1	Superior vena cava (1)	1	Near superior vena cava
I. M., 13	0	30/0	+	...	Right atrium (1) Superior vena cava (1)	4	Near superior vena cava
R. W., 13	+	100/0	+	...	Right atrium (2)	"Small"	Near superior vena cava
J. S., 5	0	25/5	0	1	Right atrium (2)	2	Central
S. D., 9	+	50/5	+	...	Right atrium (1) Superior vena cava (1)	6	Central
G. M., 5	0	45/0	0	3	Right atrium (1) Superior vena cava (1)	2	Central
M. C., 10	+	60/0	0	1	Right atrium (2)	4	Central
F. S., 10	+	35/5	+	0	Right atrium (2)	12	Central

* Numbers in parentheses refer to the number of anomalous veins at this site (either superior vena cava or right atrium).

surgically in six patients with a pressure gradient over 50 mm. Hg. In the others, the gradient was reduced but not eliminated by closure of the atrial defect alone, and in four the surgeon noted a persistent thrill over the base of the pulmonary artery.

Atrial Septal Defect with Partial Anomalous Pulmonary Venous Drainage. Partial anomalous pulmonary venous drainage to the right atrium or the superior vena cava was associated with a secundum atrial septal defect in ten patients. In each case the right pulmonary veins were at fault. The atrial septal defect was often small; it was located at the entrance of the superior vena cava ("sinus venosus" defect) in five patients and in the centre of the septum in the other five. (Table IV.)

No distinctive features were found which permitted recognition of this anomaly prior to cardiac catheterization, although the incidence of cyanosis with exertion, and of pulmonary hypertension, was greater than in isolated atrial septal defect. Roentgenograms of the chest were reviewed but the anomalous veins could not be seen even when their site of entry was known. Planigrams were not obtained.

At cardiac catheterization the pulmonary vein draining into the superior vena cava was probed in all but one patient in whom the catheter was not passed into the superior vena cava. When the veins entered at atrial level it was more difficult to be certain that their connection was anomalous. Indirect evidence was obtained by differential dye dilution studies [*8*] in one patient. In two others a mean pressure gradient of 3 mm. Hg or more across the atrial septum in the presence of a large left-to-right shunt suggested a small atrial septal defect and partial anomalous pulmonary venous drainage.

Atrial Septal Defect and Mitral Stenosis. Atrial septal defect and mitral stenosis (Lutembacher's syndrome) occurred in two patients. The mitral stenosis was of congenital origin in one (six years of age), but the cause was uncertain in the other (thirteen years of age). No history of rheumatic fever was obtained. Both patients

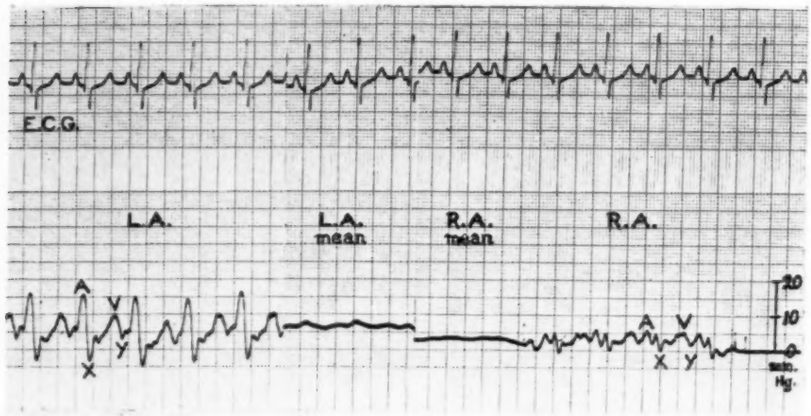


FIG. 3. Consecutive pressure tracings from left and right atrium in patient with atrial septal defect and mitral stenosis showing mean pressure gradient of 4 mm. Hg. Note prominent A wave recorded in left atrium (L.A.) but not seen in right atrium (R.A.).

were limited by fatigue and dyspnea on exertion but neither congestive failure nor atrial fibrillation had occurred. On physical examination the outstanding feature was the extreme accentuation of the first heart sound, which was readily palpable at the apex of the heart. Even in the pulmonary area the first sound was louder than the pulmonary valve closure which, to the ear, was moderately accentuated. The mid-diastolic murmur and, in particular, the presystolic murmur were more impressive than in uncomplicated atrial septal defect. An opening snap was not heard or recorded phonocardiographically. The jugular venous pulse of one patient showed a giant A wave. A qR pattern was recorded in lead V_1 of the electrocardiogram of both patients. This was encountered only twice in 134 other patients with ostium secundum atrial septal defect. The R in V_1 exceeded 16 mm. in one patient. Left atrial hypertrophy was not detected. On fluoroscopy the cardiothoracic ratio was 0.65 in both patients and the pulmonary conus unusually prominent. The left atrium was slightly enlarged in one patient and normal in the other.

The findings at cardiac catheterization varied with the size of the atrial septal defect and the severity of the mitral stenosis. In one patient with two small defects in the atrial septum (total area approximately 2 square cm.), a pressure gradient of 4 mm. Hg was present in diastole across both the mitral valve and the atrial septum. (Fig. 3.) The left atrial pressure pulse showed a large A wave while the right atrial tracing was non-contributory. In the second patient, who had a larger atrial defect (6 square cm.), a giant A wave was present in both right and left atria with no significant gradient across the atrial septum. The left ventricle was not entered.

Atrial Septal Defect and Rheumatic Mitral Incompetence. In one patient with a secundum atrial septal defect the clinical signs of significant mitral incompetence developed following an attack of acute rheumatic fever. The mitral regurgitation was confirmed at the time of repair of the atrial defect. In contrast to patients with ostium primum atrial septal defect and mitral regurgitation, the electrocardiogram in this case showed right axis deviation (plus 130 degrees) and clockwise rotation of the frontal vector.

Atrial Septal Defect and Ventricular Septal Defect. Separate defects of the atrial and ventricular septum were encountered in fourteen patients. Heart disease was recognized within the first year of life in every case and the disability was almost always severe. In seven patients congestive failure developed and six had cyanosis with crying.

The physical signs were those of the ventricular septal defect or of pulmonary hypertension *per se*. A systolic thrill was felt in nine patients. Radiologically, the heart was always large and in ten patients the cardiothoracic ratio exceeded 0.65. The left atrium was slightly enlarged in four, and moderately enlarged in two of the twelve patients in whom this was assessed. In the electrocardiogram, tall R waves in V_1, left atrial hypertrophy, and left ventricular hypertrophy combined with right ventricular hypertrophy, were all frequent findings. The mean axis of the QRS complex resembled secundum atrial septal

TABLE V
INCIDENCE OF ASSOCIATED ABNORMALITIES IN FIFTY PATIENTS WITH OSTIUM PRIMUM DEFECTS OF THE ATRIAL SEPTUM

Type of Lesion	No. of Patients
Isolated ostium primum atrial septal defect	3*
Primum atrial septal defect with cleft mitral valve	15
Primum atrial septal defect with cleft mitral and tricuspid valves	6
Common atrium with cleft mitral valve	3
Common atrioventricular canal	23
Total	50

* One patient had, in addition, a secundum atrial septal defect and pulmonary stenosis.

defect in most instances but in five patients left axis deviation and a counterclockwise frontal vector were present.

Cardiac catheterization was performed in ten patients. The atrial septal defect was readily identified by direct probing and by the large left-to-right shunt at the atrial level. The ventricular septal defect, however, was rarely probed and in most instances no significant further rise in oxygen saturation was noted at the ventricular level. The systolic pressure in the right ventricle or pulmonary artery was at or near systemic level in every case.

OSTIUM PRIMUM DEFECTS

Ostium primum defects of the atrial septum were encountered in fifty children. The frequency of associated lesions is listed in Table v.

Isolated Ostium Primum Atrial Septal Defect. Two patients with atrial septal defects of the ostium primum type had no recognizable cleft in the mitral or tricuspid valves at surgery. There were no physical signs of mitral incompetence on examination. Radiologically, the left atrium appeared slightly enlarged in one patient and normal in the other. The electrocardiogram showed no evidence of left atrial or left ventricular hypertrophy. In one patient the mean axis of the QRS was minus 70 degrees with a counterclockwise frontal vector. In the other the axis was indeterminate (? to 10 degrees) with a flat vector loop about the horizontal plane. (Fig. 2.) At cardiac catheterization, the low

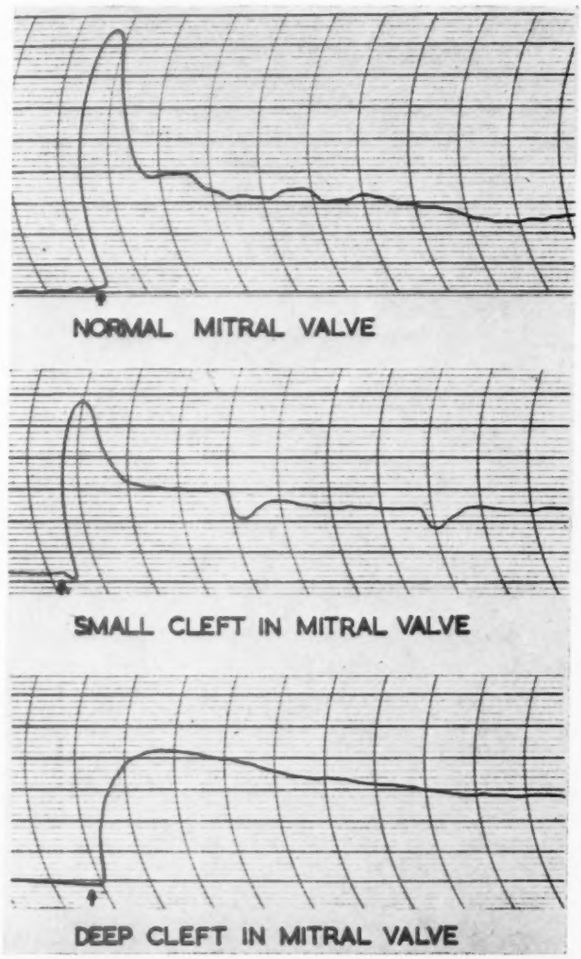
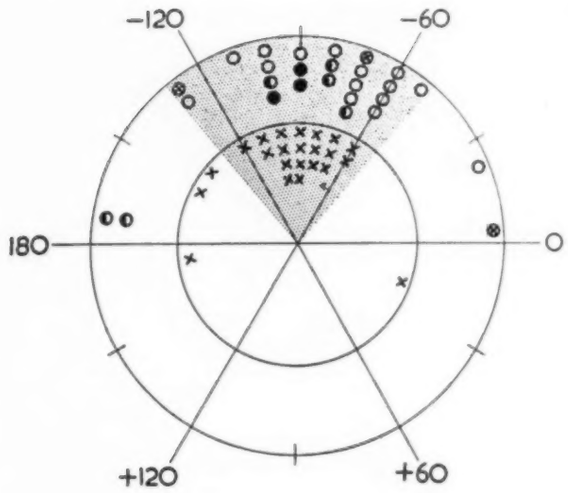


FIG. 4. Dye dilution curves recorded by ear oximetry following left ventricular injection of Cardio-Green in three patients with ostium primum defects of the atrial septum. No evidence of mitral regurgitation was noted in first patient in whom no abnormality of the mitral valve was found at surgery. In the two patients with a cleft mitral valve the dye curves suggest mild and gross regurgitation, respectively. (Arrow marks time of injection: time interval between vertical lines is ten seconds.)

position of the defect was noted in one patient. Dye dilution curves from the left ventricle were normal. (Fig. 4.)

A third patient with a small primum atrial septal defect and no deformity of the atrioventricular valves had, in addition, a moderately large secundum defect and pulmonary stenosis. The electrocardiographic axis was minus 130 degrees with a counterclockwise frontal vector. No clinical, electrocardiographic or radiologic evidence of mitral valve disease was detected, and the valve appeared normal at operation.



⊗ - - A.S.D.

○ - - A.S.D. + CLEFT MITRAL VALVE.

◐ - - A.S.D. + CLEFT MITRAL AND TRICUSPID VALVES.

● - - COMMON ATRIUM.

× - - COMMON ATRIO-VENTRICULAR CANAL.

FIG. 5. Mean axis of the QRS complex in fifty patients with ostium primum syndrome showing tendency to left axis deviation. Patients with atrial defect with or without cleft mitral and tricuspid valves are shown in outer circle and those with common atrioventricular canal in the inner circle.

Primum Atrial Septal Defect with Cleft Mitral Valve. The primum defect was associated with a cleft mitral valve in fifteen patients. Cardiac disability was more common than in isolated secundum atrial septal defect but eight of the patients had few or no symptoms. Congestive heart failure occurred in two. Cyanosis with exertion was observed in two patients and confirmed by oximetry in one. On examination, auscultatory evidence of mitral incompetence was present in eleven patients, and in nine of them a distinct left ventricular impulse was noted. In four patients a separate pansystolic murmur at the apex could not be distinguished.

The cardiothoracic ratio exceeded 0.65 in seven cases. The size of the left atrium was assessed in fourteen patients: it was moderately enlarged in four, slightly enlarged in six and appeared normal in four. The electrocardiogram showed counterclockwise inscription of the frontal vector with a mean QRS axis between minus 50 and minus 130 degrees in all but one patient who had a figure-of-eight loop with a mean axis of minus 20 degrees. (Figs. 2 and 5.) Evidence of left ventricular hypertrophy combined with right ventricular hypertrophy was found in eleven patients. Right ventricular hypertrophy alone was present in three others and the remaining patient had normal ventricular balance. Left atrial hypertrophy was seen in six.

At cardiac catheterization only one of the fifteen patients had a systolic pressure in the pulmonary artery greater than 50 mm. Hg. Left atrial pressure tracings rarely provided convincing evidence of mitral regurgitation. Dye dilution curves with left ventricular injection proved to be a better method of detecting the regurgitation. (Fig. 4.)

Primum Atrial Septal Defect with Cleft Mitral and Tricuspid Valves. Clefts of both the mitral and tricuspid valves were found in association with an ostium primum atrial septal defect in six patients. In two, very small perforations of the membranous ventricular septum were present beneath the valve leaflets. The left superior pulmonary vein and both right pulmonary veins were anomalously connected to the right atrium in one patient. In two patients congestive heart failure developed and one other showed mild cyanosis with exertion. Two patients had no symptoms.

The systolic murmur along the left sternal border was not accompanied by a thrill in any case. Physical signs of mitral or tricuspid incompetence were identified with certainty in only one patient who had a blowing pansystolic murmur at the apex of the heart but no left ventricular impulse. The second heart sound was widely split in one patient and narrowly split with marked accentuation of the pulmonary component in the other five.

Significant cardiac enlargement and dense hilar shadows were consistent radiologic findings. The cardiothoracic ratio exceeded 0.65 in two patients. The left atrium appeared moderately enlarged in one patient, slightly enlarged in two and normal in three. Electrocardiographic evidence of right ventricular hypertrophy was found in every patient; in two, it was associated with left ventricular hypertrophy. In four patients the mean axis of the QRS complex fell between minus 70 and minus 110 degrees (Fig. 5) and in each case the frontal vector was counterclockwise. In the other two patients the axis was difficult to determine (? to 170 degrees) and the frontal vector formed a figure-of-eight pattern about the horizontal axis.

TABLE VI*

ARTERIAL OXYGEN SATURATION, ELECTROCARDIOGRAPHIC FINDINGS AND RIGHT VENTRICULAR PRESSURE IN THREE PATIENTS WITH THE OSTIUM PRIMUM SYNDROME IN WHOM A COMMON ATRIUM WAS PRESENT

Patient and Age (yr.)	Cyanosis at Rest	Arterial Oxygen Saturation† (%)			Electrocardiogram					Right Ventricular Pressure (mm. Hg)
		Rest	Exertion	Breathing Oxygen	P-R Interval (sec.)	Frontal Axis p	Frontal Axis QRS	Ventricular Hypertrophy		
								Right	Left	
R. R., 11	+	80	59	92	.14	−60 degrees	−90 degrees	+	0	50/5
R. P., 4	+	78	70	85	.10	−60 degrees	−90 degrees	+	0	80/0
F. K., 8	+	93	86	...	.14	−60 degrees	−100 degrees	+	+	35/10

* Anatomic findings confirmed at surgery in two patients (R. R. and R. P.), and at necropsy in one patient (F. K.).
† Ear oximetry.

At cardiac catheterization a large left-to-right shunt was noted in each case. Moderate pulmonary hypertension was present in four patients. Atrial pressure tracings did not facilitate recognition of mitral or tricuspid incompetence.

Common Atrium with Cleft Mitral Valve. Total absence of the atrial septum, a common atrium, was associated with a cleft mitral valve in three patients. The murmur of mitral incompetence was not detected but all had left axis deviation and frank counterclockwise rotation of the frontal vector loop. Right ventricular hypertrophy was noted in two and combined ventricular hypertrophy in one.

The clinical presentation differed, however, from other ostium primum defects in two aspects. (Table VI.) First, cyanosis at rest was observed in all three patients, although this was not corroborated by ear oximetry in one patient (F. K.). Secondly, the mean axis of the p wave was minus 60 degrees in the frontal plane, whereas in all but one of the other forty-seven patients with variants of the ostium primum syndrome the mean axis fell between minus 10 and plus 80 degrees. The unusual axis and relatively short P-R interval in these three patients suggested an abnormal origin or pathway of atrial excitation, presumably due to the complete lack of septal tissue.

Common Atrioventricular Canal. In twenty-three patients a continuous deficiency of the lower portion of the septum primum and the membranous ventricular septum created a common atrioventricular canal. A secundum atrial defect was also present in four patients, pulmonary stenosis in one, and aortic stenosis in one. Eight of the group were mongoloid imbeciles. Four patients, age four to fifteen years, survived surgery. The remainder were examined at necropsy; twelve died spontaneously during the first year of life and seven, ranging in age from two months to seven years, died at surgery.

Failure to thrive was invariable. Cyanosis with crying was noted in seventeen patients and congestive failure occurred in nine. On examination, a harsh systolic murmur and thrill at the lower left sternal border was present in ten patients. In the others the murmur was soft or absent. In only one patient was mitral incompetence suspected from the physical signs. The second heart sound was usually closely split with an accentuated pulmonary component.

Radiologically, the heart was greatly enlarged, with a cardiothoracic ratio over 0.65 in twelve patients. The outflow tract of the right ventricle was particularly prominent. The left atrium was slightly enlarged in ten and moderately enlarged in one of the sixteen patients examined. A complete electrocardiogram was recorded in twenty-one patients, and standard leads only were taken in two. Combined ventricular hypertrophy was present in ten patients and right ventricular hypertrophy alone in eleven. Left atrial hypertrophy was seen in the two oldest children. The mean QRS axis lay between minus 60 and minus 140 degrees in

twenty patients; in the other three it appeared to be plus 20, plus 170 and minus 160 degrees, respectively. (Fig. 5.) However, in every case the frontal vector was counterclockwise, with the bulk of the loop above the horizontal axis.

Cardiac catheterization revealed pulmonary hypertension at or near the systemic level in nine of the seventeen patients studied; in two, pulmonary stenosis was present. A large pulmonary blood flow was demonstrated in every case.

COMMENTS

Accurate diagnosis of atrial septal defect is important for successful surgical treatment, particularly in centres where extracorporeal circulation is not routinely employed for closing these defects. The present observations in children show that in most cases the clinical findings permit recognition of the type of atrial septal defect and the presence of complicating lesions.

The electrocardiogram provides the most reliable method for differentiating ostium secundum from ostium primum defects. When the mean axis of the QRS complex lies between plus 60 and minus 150 degrees and the frontal vector rotates in a clockwise manner, the defect is almost certainly of the secundum type. Left axis deviation and a counterclockwise vector is characteristic of primum defects but very rarely a secundum defect may present these findings. When the mean axis is indeterminate and the frontal vector forms a flat loop or figure-of-eight pattern closely applied to the horizontal axis, it is not possible to designate the site of the defect from the electrocardiogram. In such cases evidence of mitral or tricuspid incompetence strongly favours a primum defect. The mean axis in common atrioventricular canal may fall beyond the range for primum defects in a few instances but counterclockwise rotation of the frontal vector, with the major portion of the loop above the horizontal axis, is a consistent finding in our experience.

The clinical features of children with secundum atrial defect follow a relatively uniform pattern. Variations from this suggest the presence of a second lesion or pulmonary hypertension. Severe disability and congestive heart failure are uncommon and cyanosis on exertion is rare. On examination, wide splitting of the second heart sound permits careful analysis of pulmonary valve closure which is of normal or slightly increased intensity. The systolic murmur is rarely accompanied by a thrill. A dominant A wave exceeding V by 3 cm. or more is not seen in the jugular venous pulse (nor in the right atrial pressure tracing at cardiac catheterization). Marked enlargement of the heart, with a cardiothoracic ratio greater than 0.65, is rarely encountered and the left atrium is seldom enlarged on fluoroscopic examination. Electrocardiographic evidence of left atrial or left ventricular hypertrophy is only seen occasionally. In lead V_1 the R wave seldom exceeds 16 mm. and a qR or Rs pattern is uncommon.

Pulmonary hypertension occurs in about 5 per cent of children with isolated ostium secundum atrial septal defect. It can be recognized by the combination of a loud pulmonary component of the second heart sound and a tall R in lead V_1 of the electrocardiogram. Other features commonly encountered include severe cardiac disability, cyanosis with exertion, a dominant A in the jugular venous pulse, and marked cardiac enlargement with unusually prominent pulmonary arteries. When the clinical findings suggest pulmonary hypertension a complicating lesion should be suspected since the incidence of pulmonary hypertension is greater when the atrial septal defect is associated with a separate ventricular septal defect or partial anomalous pulmonary venous drainage.

When pulmonary stenosis is associated with atrial septal defect and persistent left-to-right shunt its presence may be suspected by the systolic thrill and the alteration in the pulmonary component of the second heart sound. Closure of the pulmonary valve is delayed and usually soft. Less commonly, it may be loud with a snapping quality [*9*]. Cyanosis with exertion, or a dominant A wave in the jugular venous pulse may also be seen. The heart is smaller than expected with an isolated atrial septal defect and the hilar shadows may be normal or increased. In a few patients "poststenotic" dilatation of the left pulmonary artery is evident. An Rs or R pattern is frequently found in lead V_1 of the electrocardiogram, and the R wave exceeds 16 mm. in the majority of cases. If the systolic pressure gradient across the pulmonary valve is greater than 50 mm. Hg, surgical relief of the stenosis may be warranted at the time of closure of the atrial septal defect.

Partial anomalous pulmonary venous drainage cannot be recognised by clinical means in patients with atrial septal defect. It should be suspected when cyanosis with exertion or pulmonary hypertension is present. Occasionally

the anomalous veins may be seen in roentgenograms of the chest but, even in retrospect, this was not possible in the present series. At cardiac catheterization careful exploration of the superior vena cava and right atrium and dye dilution curves from the right and left pulmonary arteries serve to identify the anomalous veins in most but not all cases.

When mitral stenosis occurs with atrial septal defect it may be congenital or rheumatic in origin. The latter cause is uncommon in childhood since rheumatic mitral valve obstruction takes considerable time to develop. The physical signs draw attention to the mitral stenosis particularly when sinus rhythm is present. The mid-diastolic and presystolic murmurs are louder and the first heart sound is of remarkable intensity at the apex and in the axilla. A giant A wave may be seen in the jugular venous pulse. Radiologically, the heart is significantly enlarged and the pulmonary conus unusually prominent. The left atrium may be enlarged or normal. In the electrocardiogram, a qR pattern or dominant R pattern is seen in lead V_1. The size of the atrial septal defect may explain the variation in the physical and radiologic signs in patients with Lutembacher's syndrome [*10*]. When the atrial septal defect is large, the physical signs of mitral stenosis are less impressive, a giant A wave occurs in the jugular venous pulse and the left atrium is not appreciably enlarged on fluoroscopy. On the other hand when the defect is small the signs of mitral stenosis are striking, the jugular venous pulse is normal and the left atrium is detectably enlarged.

The clinical presentation of patients with both a secundum atrial septal defect and a ventricular septal defect is rarely confused with that of isolated atrial septal defect. Severe disability, congestive failure and cyanosis with exertion are all common and usually occur in the first year of life. A systolic murmur and thrill at the lower left sternal border or physical signs of pulmonary hypertension may be found on examination. The heart size is always markedly increased and the left atrium may be enlarged. The QRS axis and the frontal vector resemble secundum atrial septal defect in the majority of patients but the R wave in V_1 usually exceeds 16 mm. and evidence of left atrial or left ventricular hypertrophy may be present. In others left axis deviation and a counterclockwise frontal vector suggests an ostium primum defect or common atrioventricular canal.

The ostium primum group of atrial septal defects are distinguished by left axis deviation and counterclockwise rotation of the vector loop in the frontal plane. These electrocardiographic characteristics are not related to the degree of mitral incompetence since they may occur in patients with typical primum defects who have no clinical, haemodynamic or anatomic evidence of mitral incompetence. Furthermore, when rheumatic mitral regurgitation occurs in association with a secundum atrial septal defect, right axis deviation and clockwise inscription of the frontal vector are found. It would appear likely, therefore, that the distinctive pattern of electrical excitation is due to an embryologic defect in development of the conduction system. As yet we have been unable to demonstrate this anatomically.

Ostium primum defects may occur without demonstrable abnormality of the mitral or tricuspid valve. Such patients can be distinguished from patients with secundum defects only if left axis deviation and a counterclockwise frontal vector are present. Occasionally, the axis is indeterminate and the vector describes a flat loop or figure-of-eight pattern about the horizontal axis as seen in some secundum defects.

When the primum defect is associated with a cleft mitral valve, mitral incompetence is detected clinically in the majority of patients by a blowing pansystolic murmur at the apex of the heart, a left ventricular impulse, electrocardiographic evidence of left ventricular hypertrophy or enlargement of the left atrium on fluoroscopy. In some patients none of these signs is present and identification of the site of the atrial defect is dependent on the characteristic QRS axis and frontal vector.

In patients with primum defects and clefts of both atrioventricular valves, the clinical signs of mitral or tricuspid incompetence are often lacking. The electrocardiographic axis and frontal vector are typical of primum defects in most cases, but indeterminate axes and figure-of-eight or flat vector loops may be seen.

Common atrium resulting from complete absence of the atrial septum should be considered when cyanosis is noted at rest in patients with the ostium primum syndrome. Marked left axis deviation of the P wave in the frontal plane with a relatively short P-R interval was found in all three cases in this series but was not present in the electrocardiograms of two patients reported on elsewhere [*11*]. Such changes in the P wave

should arouse suspicion of common atrium since they are seldom encountered in other types of primum defect.

The clinical presentation of patients with common atrioventricular canal rarely simulates atrial septal defect. Severe disability, congestive failure and cyanosis are common, and only a few patients survive early childhood. The grave prognosis of this malformation may be exaggerated in the present series by the large number of mongoloid imbeciles. The physical signs are variable but more commonly suggest ventricular septal defect than uncomplicated atrial septal defect or mitral incompetence. The heart is markedly enlarged and in half the patients the electrocardiogram shows evidence of combined ventricular hypertrophy. The feature which links common atrioventricular canal to the various forms of ostium primum atrial septal defect is the consistent finding of counterclockwise rotation of the frontal vector above the horizontal axis.

SUMMARY

The clinical features, including electrocardiographic and fluoroscopic examination, have been reviewed in 186 patients with atrial septal defect proved at surgery or necropsy to determine whether or not the site of the defect and the presence of complicating lesions can be recognised by clinical assessment.

The electrocardiogram proved to be a satisfactory method of differentiating secundum from primum defects in all but a few patients in whom the mean axis of the QRS complex was indeterminate and the frontal vector formed a flat loop or figure-of-eight pattern about the horizontal plane.

The clinical features of ostium secundum defects followed a uniform pattern. Variation from this pattern suggested pulmonary hypertension or a complicating lesion such as pulmonary stenosis, mitral stenosis or ventricular septal defect. The presence of partial anomalous pulmonary venous drainage could not be identified prior to cardiac catheterization.

The characteristic feature of persistent ostium primum defects, with or without abnormality of the atrioventricular valves, was the counterclockwise frontal vector with left axis deviation in the electrocardiogram. When the mitral valve was cleft, clinical evidence of mitral incompetence was noted in two-thirds of the patients. Additional signs of tricuspid incompetence were lacking when both atrioventricular valves were cleft.

Common atrium was recognised by the presence of cyanosis at rest and left axis deviation of the P wave with a relatively short P-R interval.

Patients with common atrioventricular canal had the same type of counterclockwise vector loop at the ostium primum group of defects but the remainder of the clinical features more closely resembled ventricular than atrial septal defect.

Acknowledgment: We are grateful to Drs. W. T. Mustard and G. A. Trusler for reports of the findings at operation.

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The Natural History of Ventricular Septal Defects in Infancy and Childhood*

Based on Serial Cardiac Catheterization Studies

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UNTIL about ten years ago Roger's [*1*] concept of ventricular septal defect as a malformation with a characteristic murmur and no impairment of general health was widely accepted. A number of excellent articles [*2–19*] have been published since then and it is now recognized that patients with ventricular septal defects exhibit a wide spectrum of clinical and hemodynamic patterns, depending on the size of the defect and the reaction of the pulmonary vascular bed. Since repair of this malformation is now possible, with a fairly low operative mortality except in infancy, knowledge of its natural history is essential both for medical management and the proper selection of patients for surgery.

We have studied more than 450 patients with ventricular septal defects during the last thirteen years, about 95 per cent of whom were under fifteen years of age. Cardiac catheterization was performed in 140 of these subjects. The purpose of this article, an extension of previous studies from this Department [*20–22*], is to present and analyze the data of thirty-two patients who underwent serial cardiac catheterization over a period of one to seven years. Thirty-one of these patients were under fifteen years of age.

MATERIALS AND METHODS

The thirty-two patients with ventricular septal defects who form the basis of this report have had clinical, roentgenographic, electrocardiographic, phonocardiographic and angiocardiographic studies during periods of many years. There were fourteen males and eighteen females. One patient had an ostium secundum type of atrial septal defect, two had coarctation of the aorta as additional malformations. The diagnosis was confirmed at surgery in twenty patients and at autopsy in six patients. Twenty were under two years of age, ten two to six years, and two were seven and fifteen years old at the time of the first cardiac catheterization. Twenty-five were recatheterized between two and five years after the first cardiac catheterization, the rest one to seven years later. At the time of the second cardiac catheterization four were two to three years of age, sixteen three to six years, eleven six to eleven years, one was twenty-two years old. Cardiac catheterization was performed under light intravenous Pentothal® anesthesia or sedation with a combination of meperidene, Phenergan® and Thorazine.® Pressures were measured from the mid-thoracic plane by Sanborn electromanometers and recorded on a Sanborn polyviso recording apparatus. Oxygen consumption was determined when possible by collection of expired air in a Tissot spirometer and analyzed by the Scholander method of gas analysis. In the others a normal oxygen consumption was estimated by using the following formula:

$$\frac{(\text{Calorie/kilogram/twenty-four hours}) \times \text{weight (kilogram})}{1440 \times 4.8} = \text{oxygen consumed, liters/minute.}$$

Calorie/kilogram/twenty-four hours were obtained from Talbot's charts [*23*]; 1,440 is a conversion factor into minutes; 4.8 is the calorie value per liter of oxygen at a respiratory quotient of 0.8. Blood oxygen content was determined by the method of Van Slyke and Neil [*24*]. At least two blood samples were obtained from the pulmonary artery, right ventricle and right

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TABLE 1*

SERIAL CARDIAC CATHETERIZATION DATA IN THIRTY-TWO PATIENTS WITH VENTRICULAR SEPTAL DEFECT

Case No. and Sex	Age (yr.)	Body Surface Area (M^2)	Pressure (mm. Hg)						Blood Flow† (L./min./M^2)		Left-to-Right-Shunt Index (L./min./M^2)	$\frac{\text{Left-to-Right-Shunt Index}}{\text{Systemic Flow Index}} \times 100$ (%)	Pulmonary to Systemic Flow Ratio	Total Pulmonary Resistance Index (dynes/sec./$cm.^{-5}/M^2$)	Total Systemic Resistance Index (dynes/sec./$cm.^{-5}/M^2$)	Arterial O_2 Saturation (%)	Defect	
			Pulmonary Artery			Systemic Artery											Size (cm.)	Area ($cm.^2/M^2$)
			Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Pulmonary	Systemic								
1, M	1¾	0.50	20	10	16	...	...	...	6.30	4.20	2.10	50	1.5	203	...	95	...	...
	6	0.80	19	12	14	97	67	80	4.40	4.40	0	0	1.0	255	1,456	98		
2, M	15	1.50	21	11	16	86	49	58	4.34	2.97	1.37	46	1.5	295	1,560	99		
	22	1.77	20	11	15	160	100	110	2.60	1.92	0.68	35	1.4	456	4,580	94	...	...
3, F	3	0.60	23	13	19	120	87	105	6.00	3.47	2.53	73	1.7	253	2,420	95		
	5½	0.68	17	9	13	127	70	97	5.98	3.84	2.14	56	1.5	174	2,020	93	...	...
4, F	5	0.76	33	13	19	...	...	...	5.70	4.46	1.24	28	1.3	267	...	90		
	9	1.05	38	12	22	109	6	(L.V.)	11.10	4.30	6.80	158	2.6	150	...	99	...	...
5, F	19/12	0.3	25	5	(R.V.)	...	...	...	10.96	3.69	7.27	197	3.0	...	...	94		
	4	0.7	22	12	15	118	73	91	3.47	3.47	0	0	1.0	345	2,110	98	...	...
6, F	5/12	0.3	38	18	26	...	...	...	20.50	3.67	16.83	459	5.6	101	...	95		
	3	0.72	33	13	23	85	53	67	5.48	2.42	3.06	126	2.3	335	2,210	98	...	...
7, F	3/12	0.25	43	13	30	...	...	...	9.60	3.11	6.49	209	2.9	250	...	97		
	4	0.64	20	6	13	...	...	...	12.25	3.59	8.66	241	3.4	85	...	98	...	...
8, M	1¾	0.50	44	16	29	124	79	88	6.38	3.36	3.02	90	1.9	363	2,090	94		
	4	0.80	27	12	14	...	...	...	13.18	5.98	7.20	120	2.2	85	...	98	0.5 × 0.5	0.25
9, M	3	0.58	44	26	34	...	...	...	14.90	4.73	10.17	215	3.0	182	...	95		
	6	0.80	28	13	21	100	65	80	12.36	3.29	9.07	276	3.8	136	1,945	95	0.8 × 0.8	0.64
10, F	4/12	0.22	45	17	28	...	...	...	11.30	2.25	9.05	402	5.0	198	...	...		
	4	0.67	24	10	15	...	...	...	5.73	3.50	2.23	64	1.6	270	...	95	1.0 × 0.5	0.59
11, M	8/12	0.32	46	18	29	...	...	...	14.73	3.14	11.59	369	4.7	157	...	...		
	4	0.70	33	11	22	117	72	92	7.02	3.38	3.64	108	2.1	262	2,180	99	1.0 × 0.5	0.56
12, M	19/12	0.34	48	16	33	...	...	...	6.71	3.28	3.43	105	2.0	392	...	...		
	3	0.54	25	7	14	117	82	97	4.53	2.78	1.75	63	1.6	246	2,790	99	...	...
13, F	1¼	0.36	50	28	38	...	...	...	10.59	3.51	7.08	202	3.0	287	...	...		
	3	0.48	39	14	27	108	70	85	6.16	2.96	3.20	108	2.1	350	2,300	98	1.50 × 15.0	2.36
14, F	8/12	0.30	51‡	21	38	92	53	70	19.10	2.70	16.40	607	7.4	159	2,070	92		
	4	0.71	32§	10	20	116	68	73	4.73	3.62	1.11	31	1.3	338	1,610	95	0.8 × 0.4	0.36
15, M	11/12	0.36	56‖	18	41	69	3	(L.V.)	12.20	3.15	9.05	287	4.1	269	...	96		
											3.7 (LtoR)							
	4¾	0.62	15¶	6	11	83	49	61	5.59	3.23	0.4 (RtoL)	115	2.0	133	1,520	91	1.0 × 0.5	0.63
16, M	5/12	0.25	62	22	43	80	50	62	14.30	2.29	12.01	524	6.3	240	2,165	98		
	2¼	0.43	42	13	16	113	78	89	9.56	3.20	6.36	199	3.0	209	2,225	...	1.0 × 1.2	2.19
17, F	5/12	0.43	62	30	47	...	...	...	‡‡	‡‡						...		
	6	0.84	30	8	21	139	87	117	6.66	3.20	3.46	108	2.1	254	2,920	97	1.0 × 1.0	0.93
18, M	5/12	0.31	62	30	48	82	51	60	4.68	2.10	2.58	123	2.2	820	2,280	90		
	5	0.71	57	24	21	92	55	85	16.30	3.16	13.14	416	5.2	190	2,150	98	2.4 × 2.4	6.36
19, F	1¾	0.37	62	30	51	...	...	...	18.02	2.39	15.63	654	7.5	224	...	95		
	4	0.55	37	14	25	125	70	95	7.00	2.99	4.11	138	2.3	274	2,540	96	...	...

See footnotes on page 359.

TABLE 1 (*Continued*)

SERIAL CARDIAC CATHETERIZATION DATA IN THIRTY-TWO PATIENTS WITH VENTRICULAR SEPTAL DEFECT

Case No. and Sex	Age (yr.)	Body Surface Area (M^2)	Pressure (mm. Hg)						Blood Flow† (L./min./M^2)		Left-to-Right-Shunt Index (L./min./M^2)	$\frac{\text{Left-to-Right-Shunt Index}}{\text{Systemic Flow Index}} \times 100$ (%)	Pulmonary to Systemic Flow Ratio	Total Pulmonary Resistance Index (dynes/sec./cm.$^{-5}$/M^2)	Total Systemic Resistance Index (dynes/sec./cm.$^{-5}$/M^2)	Arterial O_2 Saturation (%)	Defect	
			Pulmonary Artery			Systemic Artery											Size (cm.)	Area (cm.^{2}/M^2)
			Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Pulmonary	Systemic								
20, F	3	0.66	66	41	49	...	...	...	9.91	5.08	4.83	95	1.9	395	...	93		
	6	0.84	65	36	41	105	76	91	13.10	3.68	9.42	256	3.5	246	1,975	94	1.5 × 0.5	0.70
21, F	9/12	0.37	70**	25	53	88	50	68(A)	8.08	3.58	4.50	126	2.3	524	1,518	94		
	4¼	0.68	32††	12	19	80	53	66(A)	17.60	4.26	13.34	313	4.1	86	1,240	94	1.5 × 0.5	0.87
22, F	1 3/12	0.33	73	6	(R.V.)	81	59	69	14.55	3.21	11.34	353	4.5	...	1,720	93		
	2½	0.46	73	36	57	92	60	81	7.54	3.09	4.45	144	2.5	620	2,095	98	1.5 × 0.8	2.05
23, M	6	0.79	74	49	57	81	60	66	8.50	3.25	5.25	162	2.8	536	1,620	96		
	10	0.96	76	43	55	87	67	72	9.54	2.30	7.24	315	4.1	460	2,500	92	4.0 × 2.0	6.55
24, F	3	0.52	77	35	56	...	...	...	8.64	5.88	2.76	47	1.8	518	...	90		
	6	0.68	92	57	72	97	72	86	4.00	2.60	1.40	53	1.5	1,440	2,640	95	2.6 × 2.0	4.62
25, F	5½	0.59	77	51	63	86	5	(L.V.)	9.49	3.42	6.07	178	2.7	532	...	92		
	7	0.88	82	54	65	92	63	78	7.50	2.40	5.10	213	3.1	696	2,600	94	2.5 × 2.5	5.58
26, F	6	0.70	77	47	64	99	52	67	9.26	3.30	5.96	181	2.8	552	1,620	...		
	10	0.96	103	66	77	115	77	90	7.70	3.19	4.51	141	2.4	800	2,255	90	...	...
27, M	1⅛	0.34	78	32	55	103	59	84	5.88	2.06	3.82	185	2.8	748	3,200	95		
	3	0.68	77	34	53	112	66	90	5.94	2.81	3.13	111	2.3	714	2,500	93	...	...
28, F	5	0.71	81	49	59	96	62	81	7.83	3.49	4.34	124	2.2	603	1,850	94		
	7	0.98	56	23	37	104	69	77	8.42	3.31	5.11	154	2.6	351	1,860	99	...	...
29, M	1	0.41	84	31	58	102	57	74	11.90	3.84	8.06	210	3.1	390	1,540	96		
	5	0.74	76	32	56	112	66	72	11.70	3.11	8.59	276	4.7	304	1,850	96	2.5 × 2.5	6.64
30, M	3½	0.55	93	51	70	91	57	74	8.13	3.55	4.58	129	2.3	728	1,670	93		
	5½	0.67	89	54	66	99	66	81	6.76	3.02	3.74	123	2.2	752	2,142	96	1.8 × 1.8	3.80
31, F	7	0.71	97	49	82	109	79	89	10.00	2.10	7.90	376	4.7	624	3,390	99		
	11	0.94	94	40	70	96	64	80	9.02	3.59	5.43	151	2.5	620	1,780	93	2.0 × 2.0	3.34
32, M	1½	0.48	111	54	78	...	...	...	8.60	2.86	5.74	201	3.0	722	...	...		
	2½	0.56	98	42	64	...	...	...	11.18	4.26	7.66	180	2.6	450	...	90	3.5 × 1.0	4.69

NOTE: R.V. = right ventricle; L.V. = left ventricle; A = aorta; Inf = infundibulum.

* Right-to-left shunts have not been calculated for patients with arterial oxygen saturation between 94 per cent and 90 per cent, except in Case 15 in which the angiocardiogram revealed a right-to-left shunt.

† The oxygen consumption was determined directly in the first and second catheterization in Case 2 and in the second catheterization in Case 4 and Case 31. In the rest a theoretical normal oxygen consumption was used.

‡ = 52/3 (R.V.)

§ = 78/3 (R.V.), 28/0 (Inf)

‖ = 66/6 (R.V.)

¶ = 89/2 (R.V.), 17/0 (Inf)

** = 83/0 (R.V.)

†† = 77/3 (R.V.), 46/5 (Inf)

‡‡ = Capacity not obtained due to technical difficulties.

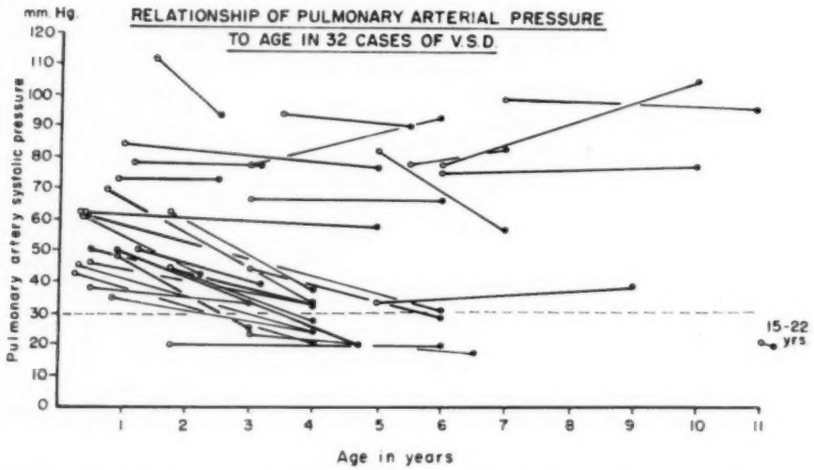

FIG. 1. Changes in the pulmonary artery systolic pressure with increasing age. Note the tendency for the pulmonary arterial pressure to fall with increasing age in patients with mild and moderately severe pulmonary hypertension.

atrium, and one from the superior and the inferior vena cava. A femoral arterial sample was obtained whenever possible. Calculation of blood flows was based on the Fick principle [*25,26*] and calculation of resistances was based on the application of standard formulas [*27*]. In common with other authors [*7,17*] we recognize the difficulties inherent in this method of estimating blood flows and resistances, particularly in infants and young children. In order to compare persons of different size, blood flows and resistances have been related to the body surface area and expressed as an index (per M^2). The total pulmonary resistance index has been used rather than the pulmonary arteriolar resistance because pulmonary wedge pressures could not be obtained on all patients. Pulmonary venous oxygen saturation has been assumed to be 96 per cent of capacity. Systemic pressures were obtained by the cuff or flush method, but only intraarterial pressures have been included in our data. Only patients who had an increment of at least one volume oxygen content at the ventricular and pulmonary artery levels at the time of the first cardiac catheterization were included in this study.

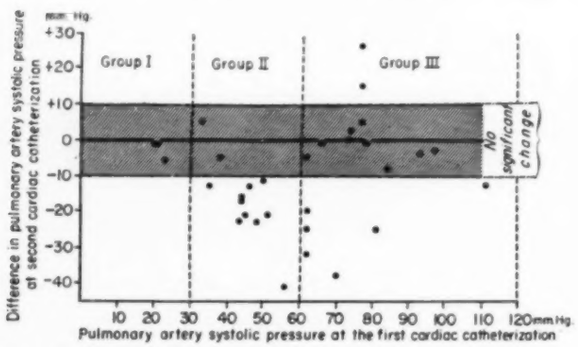
Group I
Group II
Group III
No significant change
Difference in pulmonary artery systolic pressure at second cardiac catheterization
Pulmonary artery systolic pressure at the first cardiac catheterization

FIG. 2. Original pulmonary artery systolic pressure related to the difference in pressure at the second cardiac catheterization. Black circles in zone between plus 10 and minus 10 indicate no significant change. Circles below minus 10 indicate a fall and circles above plus 10 indicate a rise in pressure.

OBSERVATIONS

Study of the changes in the pulmonary artery systolic pressure with increasing age (Fig. 1) reveals a decrease in pressure in sixteen patients, an insignificant change in fourteen, and a rise in two patients only. A comparison of the pulmonary artery systolic pressures at the first and second cardiac catheterization (Fig. 2) reveals that in three patients with a pressure below 30 mm. Hg no significant change occurred. Of twelve patients with a pressure between 30 and 60 mm. Hg the pressure fell in ten and remained virtually unchanged in two. Of seventeen patients with a pressure in excess of 60 mm. Hg the pressure fell in six, remained virtually unchanged in nine, and rose in only two patients. Based on these findings we divided our patients into three groups according to the pulmonary artery systolic pressure at the time of the first cardiac catheterization. Group I includes those with normal pulmonary arterial pressure, group II those with mild and moderate pulmonary hypertension (pulmonary artery systolic pressure between 30 and 60 mm. Hg), and group III, those with more severe pulmonary hypertension and a systolic pressure in excess of 60 mm. Hg.

Group I. Three patients (Cases 1, 2 and 3) with pulmonary artery systolic pressures below 30 mm. Hg exhibited the hemodynamic changes encountered with small ventricular septal defects.

The mean pulmonary flow was about one and a half times the systemic flow. The total pulmonary resistance index, the systemic flow index and the peripheral arterial oxygen saturation were within normal limits. (Table I.)

Recatheterization after intervals of two and a half, four and seven years revealed no rise in the pulmonary arterial pressure. The findings are summarized in Table II. It may be noted that although the mean pulmonary flow index and left-to-right shunt also decreased somewhat, the difference was not statistically significant. In one patient (Case 1) there was no evidence of a left-to-right shunt at the second cardiac catheterization. Physical examination of this patient revealed a considerable decrease in the intensity of the systolic murmur during the interval of four years between the first and second cardiac catheterization. We do not exclude the possibility that a left-to-right shunt may nevertheless be present.

Group II. The pulmonary artery systolic pressure measured between 30 and 60 mm. Hg at the first cardiac catheterization in twelve patients (Cases 4 through 15). Eight were less than twelve months of age, two were between one to two years, and two were three and five years of age. The hemodynamic findings are summarized in Table III. The average pulmonary flow was nearly three and a half times the systemic flow. The largest pulmonary blood flows were found in this group. Statistical analysis revealed no significant correlation between the pulmonary artery systolic pressure and the pulmonary flow index ($r = 0.16$). The average systemic blood flow was normal. There was no evidence of any right-to-left shunt in any of these patients. The total pulmonary resistance index was in the normal range (up to 300 dynes/second/cm.$^{-5}$) and only slightly elevated in two patients. In two patients (Cases 11 and 15) heart failure developed during the first year of life and both of them recovered with medical management.

Recatheterization after intervals of approximately two to four years revealed a fall in the pulmonary arterial pressure in ten of the twelve patients in this group. In two patients (Cases 14 and 15), to be described more fully later, the fall was associated with the development of a pressure gradient at the level of the right ventricular outflow tract. In the other eight the pressure fell between 11 and 23 mm. Hg. In the two remaining patients there was a pressure change of only

TABLE II*

SUMMARY OF SERIAL HEMODYNAMIC DATA IN THREE PATIENTS (CASES 1 TO 3) WITH PULMONARY ARTERY SYSTOLIC PRESSURE BELOW 30 MM. HG AT THE FIRST CARDIAC CATHETERIZATION (GROUP 1)

Catheterization	No. of Subjects	Pulmonary Artery Systolic Pressure (mm. Hg)		Pulmonary Flow Index† (L./min./M.²)		Left-to-Right-Shunt Index (L./min./M.²)		Left-to-Right-Shunt Index / Systemic Flow Index × 100 (%)		Systemic Flow Index (L./min./M²)		Total Pulmonary Resistance Index (dynes/sec./cm.$^{-5}$/M²)	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
First	3	21	(20 to 23)	5.54	(4.30 to 6.30)	2.0	(1.37 to 2.53)	56	(46 to 73)	3.55	(2.97 to 4.20)	250	(203 to 295)
Second	3	19	(17 to 20)	4.32	(2.6 to 5.98)	0.94	(0 to 2.14)	30	(0 to 56)	3.42	(1.92 to 4.40)	295	(174 to 456)
Difference		−2	(−6 to −1)	−1.22	(−1.90 to −0.02)	−1.06	(−2.10 to −0.39)	−26	(−50 to −11)	−0.15	(−1.05 to +0.37)	+45	(−73 to +161)
"t" test of difference		1.99		2.03		1.98		2.13		0.52		0.69	
		n.s.		n.s.		n.s.		n.s.		n.s.		n.s.	

NOTE: In this and the following tables n.s. indicates not significant.

* It is appreciated that the small number of subjects in this group detracts from the significance of the ranges. These are included to secure uniformity with the other groups, whose sizes are significant.

† Oxygen consumption determined directly in both catheterizations in Case 2.

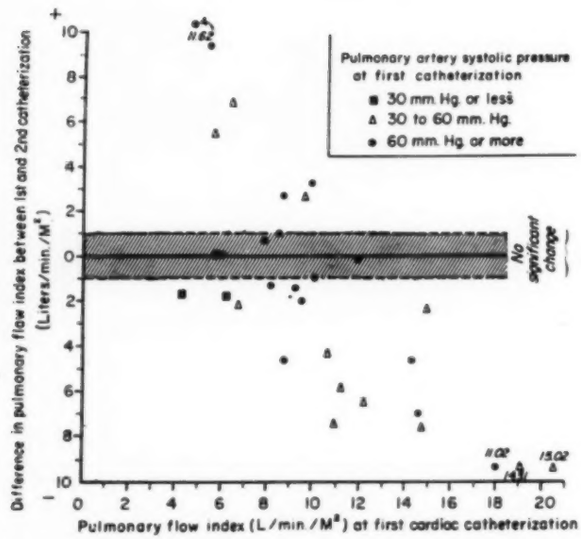
Pulmonary artery systolic pressure at first catheterization
30 mm. Hg. or less
30 to 60 mm. Hg.
60 mm. Hg. or more
No significant change
Difference in pulmonary flow index between 1st and 2nd catheterization (Liters/min./M²)
Pulmonary flow index (L./min./M²) at first cardiac catheterization

FIG. 3. Original pulmonary flow index related to the difference in the pulmonary flow index between the first and second cardiac catheterization. Note tendency for decrease in the pulmonary flow in patients belonging to group II ($t = 2.16$, $p < 0.06$).

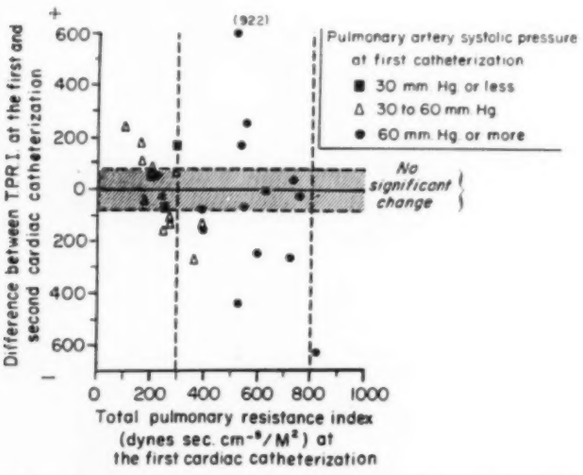
Pulmonary artery systolic pressure at first catheterization
30 mm. Hg. or less
30 to 60 mm. Hg.
60 mm. Hg. or more
No significant change
Difference between TPRI at the first and second cardiac catheterization
Total pulmonary resistance index (dynes sec. cm⁻⁵/M²) at the first cardiac catheterization

FIG. 4. Total pulmonary resistance index at the first cardiac catheterization related to the difference between the resistance index at the first and second cardiac catheterization. Resistance rose in only three patients, belonging to group III.

5 mm. Hg between the first and second studies. The pulmonary blood flow fell in nine patients and rose in three patients. The mean pulmonary flow index fell (Table III) from 11.89 L. per minute to 7.60 L. per minute, whereas the mean systemic flow index remained essentially unchanged. In order to compare the quantity of blood passing through the defect with that leaving via the aorta, the left-to-right shunt was expressed as a percentage of the systemic

TABLE III

SUMMARY OF SERIAL HEMODYNAMIC DATA OF TWELVE PATIENTS (CASES 4 TO 15) WITH PULMONARY ARTERY SYSTOLIC PRESSURE BETWEEN 30 AND 60 MM. HG AT THE FIRST CARDIAC CATHETERIZATION (GROUP II)

Catheterization	No. of Subjects	Pulmonary Artery Systolic Pressure (mm. Hg)		Pulmonary Flow Index* (L./min./M²)		Left-to-Right-Shunt Index (L./min./M²)		$\frac{\text{Left-to-Right-Shunt Index}}{\text{Systemic Flow Index}} \times 100$ (%)		Systemic Flow Index (L./min./M²)		No. of Subjects†	Total Pulmonary Resistance Index (dynes/sec./cm.⁻⁵/M²)	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range		Mean	Range
1	12	41	(33 to 56)	11.89	(5.7 to 20.5)	8.47	(1.24 to 16.83)	264	(28 to 607)	3.42	(2.70 to 4.73)	11	239	(101 to 392)
2	12	28	(15 to 39)	7.60	(3.47 to 13.18)	4.20	(0 to 9.07)	118	(0 to 275)	3.54	(2.42 to 5.98)	11	218	(85 to 350)
Difference		−13	(−41 to +5)	−4.29	(−15.02 to +6.80)	−4.27	(−15.29 to +5.56)	−146	(−577 to +130)	+0.12	(−1.44 to +2.62)	...	−21	(−278 to +234)
"t" test of difference		5.8		2.16		2.25		3.05		0.42		...	0.40	
		$p < 0.001$		$p < 0.06$		$p < 0.05$		$p < 0.02$		n.s.			n.s.	

* Oxygen consumption determined directly at second catheterization in Case 4.
† In Case 5 pulmonary artery not entered at first catheterization.

blood flow. A marked decrease in this ratio to somewhat less than half its original value was noted. This was statistically significant. (Table III.) The mean total pulmonary resistance index did not change significantly. It fell in five, rose in three, and did not change significantly in three others. (Fig. 4.) In one patient the resistance could not be obtained at the first study but was slightly elevated at the second.

In one patient in whom no evidence of a shunt was demonstrable at the second cardiac catheterization, clinical examination revealed disappearance of a thrill and decrease in the intensity of the murmur in the three year interval between the first and second cardiac catheterization.

Surgery was performed in seven of the twelve patients. The diameter of the ventricular septal defects, determined at the time of surgery, ranged from 0.5 to 1 cm. in six and measured 1.5 cm. in one patient.

Group III. In the remaining seventeen patients (Cases 16 to 32) the pulmonary artery systolic pressure exceeded 60 mm. Hg at the first cardiac catheterization. (Tables I and IV.) Five patients were under one year of age, four were one to two years old, seven two to six years, and one was seven years old. The mean pulmonary blood flow and left-to-right shunts were less than in the preceding group.

The ratio of the mean pulmonary to systemic blood flow was almost 3:1. However, only in two patients was the total pulmonary resistance index normal, in thirteen it averaged 592 dynes/second/cm.$^{-5}$, and it could not be obtained in two patients. The pulmonary resistance index ranged from a tenth to nearly a half of the systemic resistance. It exceeded 700 dynes/sec./cm.$^{-5}$ in three of nine patients under two years of age. In two of these the pulmonary resistance was approximately a third and a fourth of the systemic resistance, respectively, and in the third case (in which the systemic resistance was not available but the pulmonary flow was three times the systemic flow) a similar relationship between the pulmonary and systemic resistances probably existed. Five patients had heart failure in infancy. In three patients this was associated with a marked increase in pulmonary flow and in two with a moderately elevated pulmonary resistance. All five recovered with medical management.

Recatheterization was performed after an interval of one to two years in six patients and two to five years in eleven. The hemodynamic

TABLE IV

SUMMARY OF SERIAL HEMODYNAMIC DATA OF SEVENTEEN PATIENTS (CASES 16 TO 32) WITH PULMONARY ARTERY SYSTOLIC PRESSURE IN EXCESS OF 60 MM. HG AT THE FIRST CARDIAC CATHETERIZATION (GROUP III)

Catheterization	No. of Subjects	Pulmonary Artery Systolic Pressure (mm. Hg)	No. of Subjects	Pulmonary Flow Index* (L./min./M²)	Left-to-Right-Shunt Index (L./min./M²)	$\frac{\text{Left-to-Right-Shunt Index}}{\text{Systemic Flow Index}} \times 100$ (%)	Systemic Flow Index (L./min./M²)	No. of Subjects†	Total Pulmonary Resistance Index (dynes/sec./cm.$^{-5}$/M²)
1	17	77 (62 to 111)	16	9.33 (4.68 to 18.02)	6.59 (4.50 to 15.63)	229 (47 to 654)	3.28 (2.06 to 5.88)	15	544 (224 to 820)
2	17	69 (30 to 103)	16	9.55 (4.00 to 17.6)	6.42 (1.4 to 13.34)	199 (53 to 416)	3.18 (2.30 to 4.26)	15	506 (86 to 1,440)
Difference		−8 (+26 to −38)	...	+0.22 (+11.62 to −11.02)	−0.17 (+10.56 to −11.52)	−30 (+293 to −517)	−0.10 (+1.40 to −3.38)	...	−38 (+922 to −630)
"t" test of difference		1.86	...	0.24	0.31	0.05	0.58	...	0.47
		n.s.		n.s.	n.s.	n.s.	n.s.		n.s.

* In Case 17 flows not obtainable at first catheterization.
† In Case 22 the pulmonary artery not entered at first catheterization.

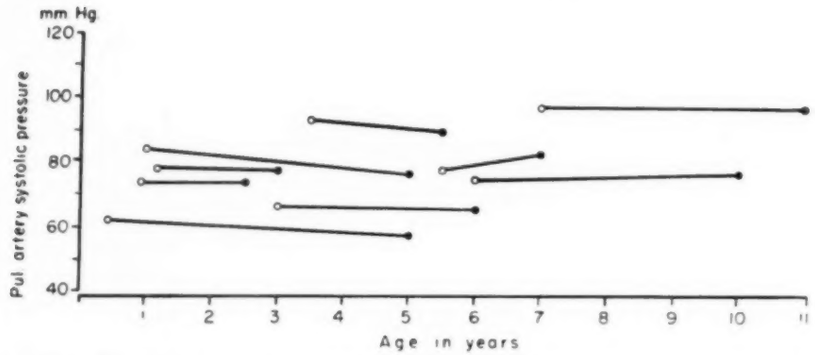

FIG. 5. Relationship of pulmonary artery systolic pressure to age in nine patients belonging to group III in whom the pressure did not change significantly.

changes are summarized in Table IV. The change in mean pulmonary artery systolic pressure was not significant. The pressure decreased in six patients, rose in two, and changed by less than 10 mm. Hg in nine. In one patient the decrease in pulmonary arterial pressure was due to the development of right ventricular outflow tract obstruction. In three patients with pulmonary artery systolic pressures of 62 mm. Hg the pressure fell considerably, to normal or near normal levels. In two patients with severe pulmonary hypertension the pressure fell; however it remained markedly elevated in one (Case 32) and moderately elevated in the other (Case 28). The pulmonary systolic pressure exceeded 70 mm. Hg in seven of the nine patients whose pulmonary arterial pressures remained essentially unchanged. (Fig. 5.)

In two patients (Cases 24 and 26) the pulmonary pressure rose by 15 and 26 mm. Hg, accompanied by a slight decrease in the pulmonary/systemic flow ratio and a rise in the total pulmonary resistance index; this latter was marked in one, although even in this case it was only approximately half of the total systemic resistance. (Table I and Fig. 4.) Surgery was successfully performed on this patient and she has been doing very well since the operation. Until this time permission for surgery has been refused for the other patient.

The mean pulmonary flow index did not change significantly (Table IV); it fell in seven patients, increased in four, and changed by about 1 L. in five patients. (Fig. 3.) In the one remaining patient flows were available at the second catheterization only. The mean left-to-right shunt index and the left-to-right shunt systemic flow ratio similarly remained essentially unchanged. (Table IV.)

The mean total pulmonary resistance index did not change significantly. The resistance decreased in five, changed by about 80 dynes/second/cm.$^{-5}$/M^2 in six, and increased in three patients. (Fig. 4.) Normal resistance was noted in more patients at the second cardiac catheterization than at the first catheterization. The systemic resistance index rose in five patients, changed by less than 100 dynes in two, and decreased in four. In the remaining cases the systemic resistance was not available for comparison. In no case did the pulmonary resistance exceed the systemic resistance, in fact the highest pulmonary resistance encountered (Case 24) was only 55 per cent that of the systemic resistance. A marked decrease in pulmonary blood flow occurred in three patients and a decrease in resistance in the other two.

Surgery was performed in thirteen patients. The diameter of the defect measured 1 cm. in one patient, between 1 and 1.5 cm. in four, between 1.5 and 2 cm. in three, and over 2 cm. in five. The largest defect measured 4 by 2 cm. in diameter.

Infants with Findings of Ventricular Septal Defect in Whom Infundibular Stenosis Subsequently Developed. In three of the thirty-two patients who originally had findings of uncomplicated ventricular septal defect a pressure gradient at the level of the right ventricular outflow tract subsequently developed. Two of these (Cases 15 and 21) have been previously reported [*20*]. All three patients were under one year of age at the time of the first cardiac catheterization. (Table I and Fig. 6.)

One patient (Case 15) was first studied, at the age of eleven months. The right and left ventricular systolic pressures were almost equal and the systolic pressure in the pulmonary artery meas-

ured 56 mm. Hg, 10 mm. Hg less than the pressure in the right ventricle. The small pressure gradient between the right ventricle and pulmonary artery was associated with a high pulmonary flow, which was four times the systemic flow. The total pulmonary resistance index was normal and the arterial oxygen saturation measured 96 per cent. A venous angiocardiogram revealed blanching of the right ventricular outflow tract and prolonged opacification of the pulmonary artery, findings commonly seen in ventricular septal defect. Cardiac catheterization three years and eight months later revealed a further rise in the right ventricular pressure and a marked pressure gradient at the level of the right ventricular outflow tract. The pressure in the main right ventricle measured 89 mm. Hg, in the outflow tract 17 mm. Hg, and in the pulmonary artery 15 mm. Hg. These findings strongly suggested the development of infundibular pulmonary stenosis. A bidirectional shunt, predominantly left to right, and a decrease in the peripheral arterial oxygen saturation from 96 per cent to 91 per cent were demonstrated. A venous angiocardiogram revealed early opacification of the aorta from a right-to-left shunt at the ventricular level. At the age of five and a half years the malformation was surgically corrected. A marked hypertrophy and displacement of the crista supraventricularis, which formed an overhanging ridge in the right ventricular outflow tract, was demonstrated. The ventricular septal defect measured 1 by 0.5 cm. diameter. The anatomic deformity of the right ventricular outflow tract was typical of that seen in tetralogy of Fallot.

A second patient (Case 21) was first studied at the age of nine months and the findings revealed evidence of ventricular septal defect with marked pulmonary hypertension. The systolic pressure in the right ventricle measured 83 mm. Hg and 70 mm. Hg in the pulmonary artery. The ratio of pulmonary to systemic blood flow was 2.3 to 1, the total pulmonary resistance index was elevated to 524 dynes/second/cm.$^{-5}$ and the arterial oxygen saturation measured 94 per cent. Recatheterization three and a half years later demonstrated the development of a considerable pressure gradient between the main right ventricle and the right ventricular outflow tract. The systolic pressure in the main right ventricle measured 77 mm. Hg; in the outflow it was 46 mm. Hg and in the pulmonary artery it was 32 mm. Hg. The pulmonary blood flow

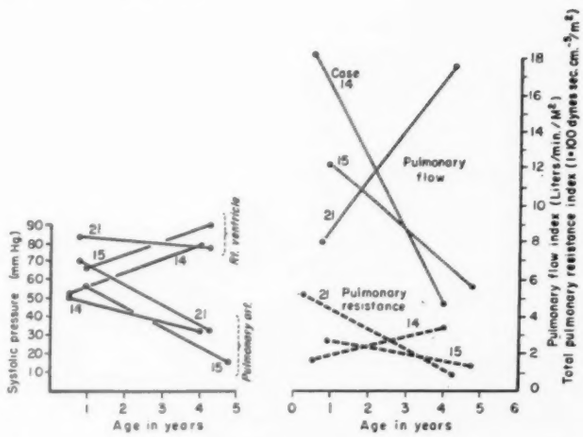

FIG. 6. Changes in right ventricular and pulmonary artery systolic pressures, pulmonary flow index and total pulmonary resistance index in three patients in whom hemodynamic evidence of infundibular stenosis developed. Note marked decrease in pulmonary arterial pressure with age. Note fall in pulmonary flow in two cases and rise in one. (See text for explanation.)

had increased considerably, the pulmonary resistance had decreased, and the peripheral arterial oxygen saturation remained at 94 per cent. The pressure gradient suggested the development of an obstruction in the right ventricular outflow tract. This, however, was not considered to be severe because the pulmonary artery systolic pressure measured 32 mm. Hg and the pulmonary blood flow was increased. Surgery performed at the age of six years revealed a ventricular septal defect which measured 1.5 by 0.5 cm. in the membranous portion of the ventricular septum and a marked deformity and obstruction of the right ventricular outflow tract. The surgeon was, however, able to pass a finger through the obstruction into the pulmonary artery. After repair of the ventricular septal defect the systolic pressure measured 106 mm. Hg in the main right ventricle, 42 mm. Hg in the outflow and 24 mm. Hg in the pulmonary artery.

In the third patient (Case 14) findings of a ventricular septal defect with a large left-to-right shunt and moderate pulmonary hypertension at the age of six months were demonstrated. Recatheterization at the age of four years revealed an increase in the right ventricular pressure, which rose from 52/3 to 78/3 mm. Hg, and the development of a pressure gradient of 50 mm. Hg between the main right ventricle and the outflow tract. The pressure in the pulmonary artery dropped from 51/21 to 32/10 mm. Hg and the pulmonary blood flow decreased

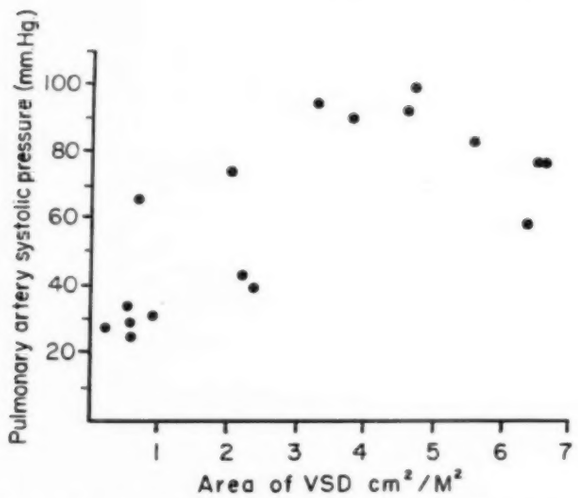

FIG. 7. Pulmonary artery systolic pressure plotted against estimated area defect (cm.²/M²) in seventeen patients with ventricular septal defect. Three patients in whom evidence of infundibular stenosis developed were not included.

markedly. The arterial oxygen saturation remained normal. Surgery demonstrated an elliptical ventricular septal defect measuring 0.8 by 0.4 cm. located high in the membranous portion of the septum below the crista supraventricularis. The latter appeared to be moderately hypertrophied. Cardiac catheterization three weeks after closure of the defect revealed no evidence of a shunt and the pressures in the right ventricle

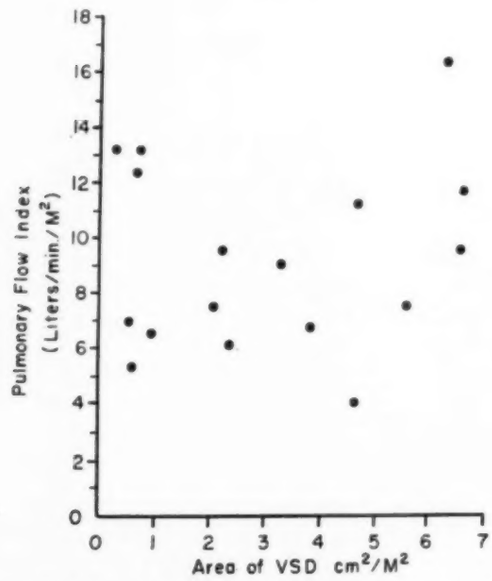

FIG. 9. Relationship of the pulmonary flow index to the area of defect in seventeen patients with ventricular septal defect (r = 0.07).

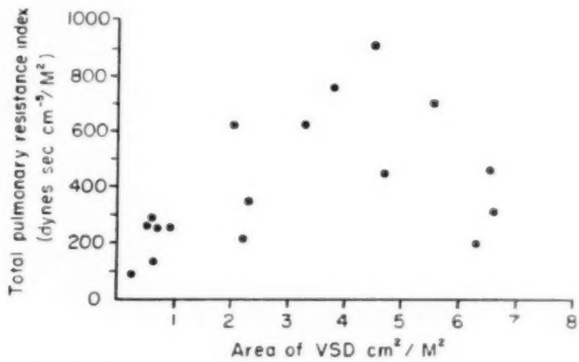

FIG. 8. Relationship of total pulmonary resistance index to area of defect in seventeen patients with ventricular septal defect (r = 0.36).

and in the pulmonary artery dropped to 31/0 and 24/9 mm. Hg, respectively.

In an additional patient with findings of ventricular septal defect in infancy findings typical of tetralogy of Fallot subsequently developed. Cardiac catheterization at two months of age revealed severe hypertension in the right ventricle and pulmonary artery. The pressure measured 85/3 mm. Hg in the right ventricle, 89/1 mm. Hg in the left ventricle and 81/28 mm. Hg in the pulmonary artery. The pulmonary blood flow was three times the systemic flow and the peripheral arterial oxygen saturation was 95.8 per cent. Recatheterization at the age of thirty-eight months revealed a marked pressure gradient between the right ventricle and the pulmonary artery. The pressure in the right ventricle measured 87/5 mm. Hg; it was 13 mm. Hg (mean) in the pulmonary artery. The peripheral arterial oxygen saturation fell to 74.3 per cent at rest. The patient died after open heart surgery for repair of the malformation and the autopsy demonstrated findings of tetralogy of Fallot.

The intracardiac anatomy of tetralogy of Fallot with hypertrophy of the crista supraventricularis and anterior deviation of the parietal band was noted in Cases 15, 21 and in the additional case. The absence of hemodynamic evidence of obstruction of the right ventricular outflow tract during infancy suggests that the obstruction due to the distortion and hypertrophy of the right ventricular outflow tract was very mild and increased in severity with increasing age. In Case 14 the obstruction was predominantly functional because normal hemodynamics were demonstrated following simple closure of the defect.

Relation of the Size of Ventricular Septal Defects to the Hemodynamics. The size of the defect was determined in twenty patients in whom open heart surgery was performed. The area of the defect per square meter body surface ($cm.^2/M^2$) was calculated from the surgeon's estimate of the dimensions of the defect. The relationship of the area of the defect to the pulmonary artery systolic pressure is illustrated in Figure 7. With only one exception, where the pulmonary artery systolic pressure measured 65 mm. Hg, patients with defects smaller than 1 $cm.^2/M^2$ had normal or near normal pulmonary artery pressures. With three exceptions, patients with larger defects had severe pulmonary hypertension. There were no patients with defects measuring between 1 to 2 $cm.^2/M^2$ in this group. Although statistical analysis revealed significant correlation between the pulmonary artery systolic pressure and the area of the defect ($r = 0.7$), no correlation existed between these two parameters in those instances in which the estimated area of the defect was larger than 2 $cm.^2/M^2$ ($r = 0.32$). There was little difference between the pulmonary and the systemic arterial pressures in six of eleven patients with defects greater than 2 $cm.^2/M^2$. In four patients the systemic pressure was greater than the pulmonary artery pressures, in the range of 35 to 71 mm. Hg, and in one patient it was only 19 mm. Hg higher.

The pulmonary resistance index was normal in patients with defects smaller than 1 $cm.^2/M^2$. (Fig. 8.) In one patient it was minimally elevated. Patients with larger defects showed wide variation in pulmonary resistance. Statistical analysis revealed no significant correlation ($r = 0.36$) between the area of the defect and the pulmonary resistance. The relationship of the pulmonary blood flow to the area of the defect is illustrated in Figure 9. A tendency to larger flows and shunts with increasing size of the defect is suggested, although large flows and shunts also occurred in patients with defects smaller than 1 $cm.^2/M^2$. Statistical analysis revealed no significant correlation between the area of the defect and the pulmonary blood flow ($r = 0.07$).

COMMENTS

Only in the last few years have recatheterization studies in patients with ventricular septal defects become available. Emphasis has been placed mostly upon changes in the pulmonary arterial pressures whereas changes in blood flow, pulmonary resistance, and especially the age of the patient, which are most important factors in evaluating the natural course of these patients, have not been stressed. Our observations during the period of infancy and early childhood reveal that some of the most important intracardiac and pulmonary vascular changes occur during this period.

One of the earliest observations on the changes in the pulmonary arterial pressures based on serial cardiac catheterization study is that of Kay, Zimmerman and Cross [*28*] of twenty-two patients with ventricular septal defects; of these patients none was under a year of age, thirteen were under ten years of age, seven were between eleven and twenty years and two were over twenty years at the time of the first cardiac catheterization. They found that most of their patients exhibited progressive elevation of the intracardiac and pulmonary arterial pressure after a period of one or two years; however, recatheterization data and calculated flows and resistances were not included in their report. During the last few years the view that patients with ventricular septal defects were in great danger of rapidly developing pulmonary hypertension and progressive pulmonary vascular disease became widespread and has been used as a strong argument for advising early surgery. Thus Lillehei [*29,30*] stated that "of all patients born with this defect in the days before surgery the overwhelming majority died prematurely. The attrition rate was particularly high during the first year of life, approaching 50 per cent in some series . . . the lethal element is, primarily the early rapid and progressive development of hypertension associated with pulmonary arterial sclerosis." Adams [*31*] reported on the physiologic changes with age in thirty patients with ventricular septal defects, and noted that thirteen patients showed signs of increase in pressure, twelve showed very slight changes, and five showed a fall in pulmonary arterial pressure. He emphasized that in many instances this was a progressive malformation. Apparently no patient had reversal of the shunt or a bidirectional shunt. The explanation for the difference in his findings and ours is probably related to the fact that two-thirds of our patients were under two years of age at the first catheterization whereas probably a much smaller proportion of his cases belonged to this age group. Brotmacher and Campbell [*15*] in their review of the natural history of ventricular septal defects state

that it would be reasonable to conclude that when the pressure is already raised early in life it rises further with age. Burchell's [*32*] views are in essential agreement with theirs but were not based on serial hemodynamic studies. Cournand [*33*] surmised "that in the young age group the (pulmonary) pressure would tend to decrease as they grow up whereas in the older age such a tendency should not be observed."

Evidence has, in fact, been accumulating that rapidly progressive pulmonary hypertension is not a common complication of ventricular septal defect during infancy and childhood. Thus Gasul et al. [*21*] in 1957 reported regression of mild to moderate degrees of right ventricular and pulmonary hypertension to normal or near normal pressures in six of fifteen patients with ventricular septal defect, a point also emphasized in preliminary communications of some of our present findings by Weinberg et al. [*34*] and Lynfield et al. [*35*]. Recently Downing [*36*] reported serial cardiac catheterization findings in twenty patients with ventricular septal defects. Nine of these patients were under one year of age at the time of the heart catheterization. In one patient with pulmonary hypertension the pulmonary artery systolic pressure rose 12 mm. Hg. In thirteen patients the pulmonary artery systolic pressure hardly changed and in six patients the pressure dropped between 10 and 34 mm. Hg. The actual changes in flows and resistances were not reported although he indicated that the magnitude of the left-to-right shunt, as judged by the step-up in oxygen content from right atrium to right ventricle, was virtually unchanged in all except three cases in which a significant reduction was observed.

Of the group of thirty-two patients herein described, twenty were under two years, ten were between two to six years, and two were seven and fifteen years of age at the first catheterization. Pulmonary hypertension was present in all but three patients initially. At the second cardiac catheterization the pulmonary arterial pressure had decreased in sixteen patients; in three this was associated with the development of a pressure gradient at the right ventricular outflow tract after an interval of three to four years. In fourteen patients the pulmonary arterial pressure changed only very slightly. Nine of these had considerable pulmonary hypertension and five had normal or minimally elevated pulmonary arterial pressures. Only two of the thirty-two patients showed a rise in the pulmonary arterial pressure. Our experience thus indicates a definite tendency for the pulmonary arterial pressure to decrease with age. This is evident if the first cardiac catheterization is performed before the age of two years. In patients with severe pulmonary hypertension and in those with normal or slightly elevated pulmonary artery pressures initially, the pressure tended to remain substantially unchanged during the period of observation. We have noted no tendency for the pulmonary arterial pressure to rise with age in patients with initial normal pressures. At approximately two to four years of age the pulmonary arterial pressure tends to stabilize to either normal or near normal levels, particularly in patients with mild to moderate pulmonary hypertension. The pressure may also fall, although to a lesser extent, in those with severe pulmonary hypertension.

The explanation for these phenomena is not established but several theories may be postulated. The rapid increase in heart size during the first few years of life, especially the first year, is well known. Whether or not the defect undergoes a corresponding increase in size has not been ascertained. It is very likely that the fall in pulmonary arterial pressure and the decrease in pulmonary blood flow are due to a relative decrease in the size of the defect, which tends to maintain its original size as the heart grows larger. Another related factor is the increasing capacity of the pulmonary vascular bed, which in turn depends largely upon the normal regression of the fetal type of vasculature. Since our data suggest that the fall in pressure tends to occur after the first year of life, it is probable that these regressive changes in the pulmonary vessels are delayed. One patient (Case 21) illustrates this assumption because in the original study performed at the age of nine months the calculated total pulmonary resistance was considerably elevated. At the second study performed at the age of four years and three months the pulmonary blood flow had increased markedly, in the face of some obstruction at the right ventricular outflow tract, and the calculated pulmonary resistance dropped to a normal level. These findings suggest that the elevated pulmonary resistance in the first study could be ascribed to the still unregressed fetal state of the pulmonary vasculature which subsequently underwent delayed regression as evidenced by the increased pulmonary blood flow and normal pulmonary resistance in the

second study. A further possible additional factor to account for these changes is the increasing capacity of the pulmonary vascular bed associated with normal growth.

The high incidence of mild to moderate pulmonary hypertension in patients below two years of age can probably be explained similarly by these two interrelated factors. The marked increase in pulmonary flow associated with a relatively larger ventricular septal defect in infancy throws a great burden on the heart which may result in heart failure. The subsequent fall in the pulmonary blood flow and pulmonary arterial pressure probably accounts for the improvement which has been observed clinically after the first year of life [*20*].

In the four patients with severe pulmonary hypertension studied in the first eighteen months of life in whom no significant change in pulmonary arterial pressure occurred, the pulmonary blood flow either increased, decreased or remained virtually the same, probably depending on the extent of the regressive changes in the pulmonary vasculature. Although the defect may have become somewhat smaller in relation to the increasing heart size, it remained critically enlarged. The data in Figure 7 substantiate this assumption since they demonstrate severe pulmonary hypertension of almost the same order as in those patients with the largest defects. Similar observations relating the size of the defect to the pulmonary artery pressure were well demonstrated by Swan, Savard and Kirklin [*13*].

The pulmonary resistance in this series fell in ten cases, remained virtually unchanged in twelve, and increased in seven. In four of the latter the rises represented an increase from a low normal to an upper normal or slightly elevated level and were accompanied by a considerable decrease in the volume of the shunt. In the other three patients, in whom marked pulmonary hypertension was present initially, the rise was accompanied by a slight decrease in the pulmonary to systemic flow ratio in two, and a slight increase in one. These findings suggest that in cases with ventricular septal defect with increasing pulmonary resistance, this is an insidious process progressing over many years. Where this has occurred the pulmonary blood flow remained at least one and a half times that of the systemic blood flow and no significant right-to-left shunt occurred. In other words, the patients remained operable from a surgical point of view [*39*]. In our experience, infants with the clinical findings of a large ventricular septal defect associated with severe pulmonary hypertension, a considerable increase in pulmonary resistance, and a bidirectional shunt usually turn out to have partial transposition of the great vessels in addition to their ventricular septal defects.

The average systemic blood flow index remained in the range of normal even in the group of patients with a marked increase in pulmonary blood flow. A rise in systemic arterial pressure or resistance was not consistently accompanied by a corresponding increase in pulmonary blood flow as anticipated [*8*].

The suggestion that ventricular septal defects may close spontaneously was first made by Parkes-Weber [*37*]. Lev [*38*] described a case in which closure of a small defect almost certainly occurred. Further evidence in support of the view that defects may become smaller are two of our patients in whom the systolic murmur decreased in intensity to a significant degree and no shunt was demonstrable at the second cardiac catheterization. One of the authors (B. M. G.) has seen in consultation at least four children who initially had a grade III to IV (Levine's classification) "puffy" systolic murmur at the third and fourth left intercostal spaces close to the sternum, and this murmur completely disappeared after a period of four to five years. It is possible that these patients had a small ventricular septal defect in the lower muscular portion of the septum which became functionally and possibly even anatomically obliterated.

It is now possible to offer an explanation for the development of the manifestations of infundibular pulmonary stenosis in four patients who originally had the findings of ventricular septal defect. These patients at the time of surgery were noted to have an abnormal crista supraventricularis. In three patients the septal and parietal bands of the crista supraventricularis were thickened and distorted, as seen in cases of tetralogy of Fallot. These findings suggest that the hemodynamic transformation from ventricular septal defect with pulmonary hypertension to ventricular septal defect with infundibular pulmonary stenosis depends upon the gradual development of increasing obstruction of the right ventricular outflow tract caused by the distorted or abnormally situated and hypertrophied crista supraventricularis. The heart may already have the morphologic char-

acteristic of tetralogy of Fallot during infancy, but the obstruction in the right ventricular outflow tract may not be sufficiently severe to be detectable by cardiac catheterization until, as the obstruction progresses with age, the typical clinical and hemodynamic manifestations of tetralogy of Fallot become evident. In one patient the crista was only slightly thickened and the evidence of obstruction of the right ventricular outflow tract was not detected in the cardiac catheterization performed within three weeks following closure of the ventricular septal defect. The obstruction in this patient was presumably predominantly functional in nature, perhaps somewhat analogous to that noted on the left side of the heart in cases of "functional" aortic stenosis reported by Morrow and Braunwald [*40*].

The results of this study suggest that surgical closure of ventricular septal defects should rarely be attempted before the second or third year of life. This gives the patient the advantage of allowing the natural tendency for the pulmonary arterial pressure and flow to decrease and at the same time avoid the risks of surgery in infancy. The recommendation of early surgery in infancy and early childhood for fear of the development of rapidly progressive, irreversible pulmonary vascular changes is not justified. No death in uncomplicated cases of ventricular septal defect receiving continuous digitalis and antibiotic treatment was noted in our series of patients. Patients with small ventricular septal defects have an excellent prognosis, and surgery in these cases is not recommended until the operative mortality is sufficiently low to justify the risk.

SUMMARY AND CONCLUSIONS

Over 450 patients with ventricular septal defect have been studied during the past ten years to determine the natural course of the disease, 140 by cardiac catheterization. In thirty-two patients, who form the basis of this report, serial cardiac catheterizations have been performed. Of these, twenty were below the age of two years, eleven were between two and seven years, and one was fifteen years old at the time of the first cardiac catheterization. The interval between the first and second cardiac catheterization in twenty-six patients was two to five years, and one to seven years in the remainder.

A high incidence of pulmonary hypertension associated with a marked increase in the pulmonary blood flow was noted in the first two years of life. The pulmonary arterial pressure decreased in sixteen of the thirty-two patients. A marked tendency for the pulmonary blood pressure and flow to decrease after the first year or two of life was noted, especially in those with initial mild and moderate pulmonary hypertension.

In three patients and in another case not included in the present series manifestations of infundibular pulmonary stenosis appeared, due to the development of a pressure gradient at the right ventricular outflow tract. At surgery there was hypertrophy of the crista supraventricularis in one, and in the other three cases it was also accompanied by the typical anterior deviation of the parietal band seen in tetralogy of Fallot.

A progressive rise in pulmonary resistance associated with severe pulmonary hypertension was noticed only in three patients, who already had a considerably elevated pulmonary resistance at the time of the first cardiac catheterization. In all three patients the pulmonary flow remained in excess of the systemic flow and no significant right to left shunt occurred. No patient with normal or slightly elevated pulmonary resistance at the time of the first catheterization subsequently had a marked increase in resistance.

These studies demonstrate that in ventricular septal defect there is a definite tendency for the pulmonary artery pressures to fall after the first or second year of life, and that there is no evidence for rapidly progressing and irreversible pulmonary hypertension in early childhood. The point is important in relation to surgical intervention.

Acknowledgment: We gratefully acknowledge the help of Dr. E. H. Fell, Attending Cardiovascular Surgeon, Cook County Hospital and his Associates Drs. M. Weinberg, A. Gordon, Z. Steiger and F. Johnson for the surgical data included in this paper.

We also wish to extend our thanks and appreciation to Dr. Sheldon S. Waldstein, Assistant Professor of Medicine, Northwestern University for the statistical analysis of our data.

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Clinical and Hemodynamic Features of Advanced Rheumatic Mitral Regurgitation*

Review of Sixty-Five Patients

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THE present report deals with the clinical and hemodynamic findings in sixty-five cases of advanced rheumatic mitral regurgitation. Surgery for correction of mitral insufficiency was performed in sixty-four patients, two of whom underwent an autopsy. In one case postmortem confirmation alone was obtained. In all the patients in whom surgery was performed the amount of regurgitation was estimated by the surgeon to be greater than 2 plus (based on a grading system of 0 to 4 plus). The area of the mitral valve was at least 1½ fingers (2.5 cm.²) in size in seventeen patients and between 2 fingers (4 cm.²) and 3½ fingers in the remaining. An area of 2.5 cm.² is well beyond the critical size of dynamically significant mitral stenosis.

TABLE I*
CLINICAL FEATURES

Incidence of rheumatic fever	80
Average age at the time of first attack	11.4
Average age at which a murmur was discovered	14.3
Average asymptomatic interval	10.6
Fatigue	94
Exertional dyspnea	91
Palpitation	46
Orthopnea	46
Paroxysmal nocturnal dyspnea	37
Cough	33
Chest pain of any type	27
Ankle edema	23
Hemoptysis	18
Vertigo	17
Embolization	7

* Clinical features stated in per cent; age and asymptomatic interval stated in years.

RESULTS AND DISCUSSION

Clinical Features (*Table I*). Of the sixty-five patients studied, forty-three were female and twenty-two were male, a ratio of 2 to 1. Their ages ranged between thirteen and fifty-four, with a mean of thirty-three years.

Fifty-two patients (80 per cent) gave a history compatible with acute rheumatic fever; eight (12 per cent) had had chorea, the remainder experiencing other manifestations of the disease including arthritis, acute carditis and erythema marginatum. The average age at the time of the first attack was 11.4 years, with a range of three to thirty-five. Seventeen (26 per cent) suffered recurrences, of whom twelve (19 per cent) had more than one. The remainder described had as few as two and as many as fifteen flare-ups. The asymptomatic intervals (time from first attack of rheumatic fever to the development of symptoms) averaged 10.6 years in fifty-two patients. In nine (17 per cent) symptoms appeared at the time of the initial bout of rheumatic fever and persisted until the time of surgery. One patient felt well for thirty-six years prior to the appearance of fatigue and dyspnea.

Sixty-two (95 per cent) recalled the age at which a heart murmur was first mentioned to them by an attending physician. This averaged 14.3 years (range 0 to 34 years). The first symptoms to appear were invariably dyspnea and fatigue, developing in both instances 8.4 years prior to hospitalization for cardiac surgery. A total of sixty-one patients (94 per cent) eventually were troubled by shortness of breath, as compared to fifty-nine (91 per cent) with fatigue.

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Some patients were free of complaints for over two decades. Palpitation was present in thirty (46 per cent) for an average duration of 5.8 years. There was no way of determining whether or not the onset of palpitation was directly related to the appearance of atrial fibrillation. Orthopnea was noted in a similar group of patients for a mean period of 5.6 years. Twenty-four patients (37 per cent) had paroxysmal nocturnal dyspnea, five of whom had classic pulmonary edema. The disturbance was rarely repetitive, but intermittent attacks did occur for some over a span of 4.2 years prior to heart surgery. Cough was present in twenty-two patients (33 per cent). It was often dry and hacking, and frequently nocturnal and paroxysmal. Occasionally it was productive of small amounts of mucus. It was present most commonly in those with markedly distended left atrial chambers. The duration of this symptom prior to hospitalization was 3.2 years. Twelve patients (18 per cent of total) had at least one attack of hemoptysis during a two year interval before hospitalization. Frequent recurrences were noted in only two of these patients. Chest pain of almost every type was reported by eighteen patients (27 per cent). In four of these it was a retrosternal discomfort with radiation to the left arm. Vertigo was present in eleven (17 per cent), syncope in four (6 per cent).

Five patients (7 per cent) suffered a single overt embolic episode, in two to the lungs, in the remainder to the extremities. There were no cerebral vascular accidents.

Failure of the right side of the heart was a late development. Fourteen patients (22 per cent) had objective evidence of manifest failure of the right side of the heart at the time of hospitalization. None gave a history of ascites, but fifteen (23 per cent) mentioned edema of the ankles and twelve (18 per cent) fullness and pain in the epigastrium and right upper quadrant of the abdomen. The average duration of edema of the ankles was 3.1 years.

Digitalis had been administered to fifty-three patients (82 per cent), a low sodium diet to thirty-five (54 per cent), and diuretics to seventeen (26 per cent). Digitalis was usually started soon after the appearance of dyspnea and fatigue while diuretics and sodium restriction were employed later in the course of the disease.

Four patients (6 per cent) were in Class 1 of the American Heart Association Functional Classification, eight (12 per cent) in Class 2, fifty-two (80 per cent) in Class 3 and one (2 per cent) in Class 4.

On cardiac auscultation, atrial fibrillation was present in 75 per cent, the remainder had a normal sinus rhythm. A pansystolic regurgitant murmur was identified at the apex in all cases. It tended to be blowing in quality, with an intensity of Grade 3 or greater in fifty-one (78 per cent) of the group. It was widely transmitted over the precordium, with characteristic radiation to the left axilla but in those with the loudest apical murmurs transmission to the base also occurred, and in some of these the systolic murmurs were clearly audible over the posterior chest. At times it was necessary to distinguish this murmur from that produced by tricuspid regurgitation [*1*].

Mid-late diastolic murmurs were noted in forty-one patients (63 per cent). These murmurs were usually blowing, but some were rough and associated with diastolic thrills.

The first mitral sound was usually normal or dull in quality and sometimes hard to identify because of the loudness of the apical systolic murmur. In eighteen patients (28 per cent) it was actually high-pitched and sharp.

A third heart sound in diastole was a very common auscultatory finding. This gallop sound appeared synchronously with a palpable shock noted over the precordium. In twenty-four patients (37 per cent) the additional diastolic sound had all of the auscultatory characteristics of an "opening snap."

The pulmonic second sound was constantly accentuated and usually reduplicated, presumably due to earlier closure of the aortic valve. (Fig. 1.)

Normal sinus rhythm was observed only in patients with a normal ventricular complex or evidence of left ventricular hypertrophy in the electrocardiogram. Electrocardiographic evidence of left atrial enlargement was present in all cases. The axis of the QRS complex was normal or deviated to the right in most instances. In the total series, left axis deviation was present in eleven (17 per cent) patients; seven of these had left ventricular hypertrophy, four had a normal ventricular complex. The ventricular complex was normal in 50 per cent of the cases, left ventricular hypertrophy occurred in 30 per cent, right ventricular hypertrophy in 15 per cent and combined ventricular hypertrophy in 5 per cent. These observations have been presented elsewhere in greater detail [*2*].

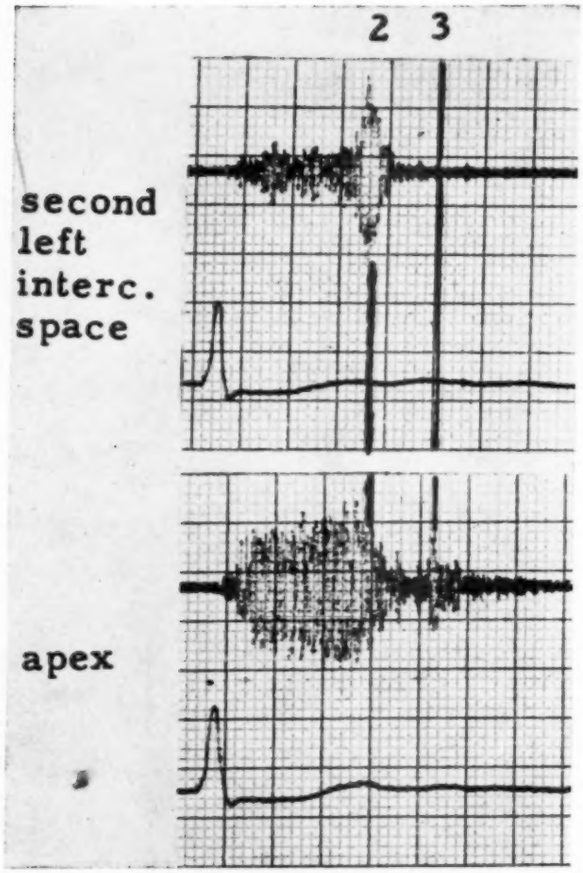

FIG. 1. High amplitude, high periodicity pansystolic murmur best recorded at the apex, fusing and overlapping with the second sound. A third heart sound is recorded in this area. At the second left intercostal space there is a second sound of high amplitude and frequency (paper speed 50 mm. per second).

FIG. 2. Appearance of the mitral valve (at autopsy), viewed from the left atrium, in a patient with rheumatic mitral regurgitation.

The roentgenograms of the chest were available for review in all but four cases. The heart size (based on a grading system of 0 to 4 plus) was normal in two (3 per cent), 1 plus in four (7 per cent), 2 plus in eleven (18 per cent), 3 plus in thirty-one (51 per cent), and 4 plus in thirteen (21 per cent).

In only four (7 per cent) was the left upper cardiac border considered normal. In the fifty-one cases in which it was prominent, a combination of pulmonary artery and atrial appendage enlargement was usually responsible. In five (8 per cent) the left atrial appendage alone produced the increase in size.

The left lower cardiac border was rounded or elongated in all but four (7 per cent). A double contour on the right cardiac border was visible in thirty-eight (62 per cent), consisting chiefly of a combination of right and left atria and right ventricle. The left atrium, on the basis of correlative measurements derived from the postero-anterior, right anterior oblique and left lateral views, was normal and indeterminate, respectively, in one patient (1.5 per cent) with no cardiac enlargement and a second with a 4 plus heart (1.5 per cent); one plus in five (8 per cent), two plus in seven (12 per cent), three plus in 32 (52 per cent), four plus in eleven (18 per cent) and five plus in four (7 per cent). Estimation of left ventricular size was difficult and required a careful study of all four projections as well as fluoroscopy. Even then problems in measurement arose, especially in the presence of a large left atrium. Despite this, significant left ventricular enlargement was thought to be present in twenty-nine (48 per cent) of the cases; the left lateral projection, as suggested by Eyler et al. [*3*] provided some help in this regard. The right ventricle, as judged from the right anterior oblique and left lateral views, was normal in eighteen (30 per cent), one plus in thirteen (21 per cent), two plus in fifteen (25 per cent), three plus in eight (13 per cent), four plus in five (8 per cent) and indeterminate in two (3 per cent). In one patient the right atrium appeared to be enlarged. The pulmonary artery, as studied in the right anterior oblique and left lateral views, was normal in only two patients. On the other hand, massive prominence of this vessel was noted in only fifteen instances (25 per cent). As one might expect from the wide variation in counterclockwise rotation of the heart, the aortic knob was normal in twenty cases (32 per cent), decreased in eighteen (30 per cent), and absent in twenty-three (38 per cent).

The pulmonary vascular markings were nor-

TABLE II*

HEMODYNAMICS IN PATIENTS WITH NORMAL SINUS RHYTHM

Subject	Age (yr.)	Cardiac Index (L./min./M²)	Pressures (mm. Hg)							Total Pulmonary Resistance (dynes second cm.⁻⁵)
			Right Atrium	Right Ventricle	Main Pulmonary Artery	"PVC"	Left Atrium	Left Ventricle	Brachial Artery	
Normal Ventricular Complex										
B. M.	21	3.9	(3)	29/2	26/8 (15)	(12)	...	...	120/70 (92)	226
M. A. S.	21	...	(0)	30/3	...	...	(12)	84/10	120/68 (84)	...
E. R.	40	...	(0)	20/4	18/4 (13)	...	...	...	...	...
Left Ventricular Hypertrophy										
M. B.	26	2.5	(0)	38/2	44/16 (25)	(17)	(21)	95/8	125/70 (80)	465
E. DeO.	29	3.6	(2)	25/3	22/6 (12)	(5)	...	..	135/60 (80)	196
H. M.	28	1.9	(−2)	19/−2	19/2 (11)	(9)	...	...	100/48 (67)	284
M. J. W.	18	2.5	(3)	30/4	35/18 (25)	(10)	...	...	120/68 (60)	488
J. D.	30	...	...	...	...	...	(21)	116/8	90/40 (60)	...
C. D.	44	1.6	(3)	19/6	18/8 (13)	...	...	...	...	490
Combined Ventricular Hypertrophy										
M. P.	13	4.0	(0)	56/1	60/28 (45)	(9)	...	...	145/75 (87)	610

* Figures in parenthesis refer to mean pressures.

mal in twenty-five patients (41 per cent), 1 plus in twenty-two (36 per cent), 2 plus in thirteen (21 per cent), and 3 plus in one (2 per cent). Calcification of the mitral valve was observed on fluoroscopy in twenty cases (33 per cent).

Pathology (*Fig. 2*). In forty-nine (94 per cent) of the patients in whom the regurgitant jet could be accurately localized at the time of surgery the predominant leak was found at the posterior commissure. In seven of this group it extended to the central part of the aperture while in six it could be felt by the surgeon at the anterior commissure as well. In two patients, it was limited to the anterior commissure.

There was evidence of calcification of the mitral leaflets in sixteen (31 per cent) of the fifty-two cases in which this observation was recorded at surgery. It was usually confined to the mural leaflet but a few patients had involvement of the septal leaflet too. In eighteen patients (33 per cent) slight degrees of anterior commissural fusion was uncovered. Only two patients had minimal posterior commissural fusion.

In six instances (12 per cent) Aschoff bodies in various stages of evolution were found on microscopic examination. Six others (12 per cent) had evidence of subendocardial fibrosis, alone, two more had perivascular fibrosis.

Hemodynamics (*Tables II and III*). On forty-one of the sixty-five patients hemodynamic studies were obtained. Right heart catheterization was performed in twenty-three, left heart catheterization in twelve, and combined left and right heart catheterization in six, according to technics already described [*4,5*].

The cardiac index, when obtained (twenty-four patients), ranged from 1.1 to 4 L./minute/M², with an average of 2. Patients with normal sinus rhythm had values ranging from 1.6 to 4, with an average of 2.9; in two of these seven the cardiac index was less than 2.6 L./minute/M². In patients with atrial fibrillation the range was 1.1 to 2.4, with an average of 1.7. The type

TABLE III*

HEMODYNAMICS IN PATIENTS WITH ATRIAL FIBRILLATION

Subject	Age (yr.)	Cardiac Index (L./min./M²)	Pressures (mm. Hg)							Total Pulmonary Resistance (dynes second cm.⁻⁵)
			Right Atrium	Right Ventricle	Main Pulmonary Artery	"PVC"	Left Atrium	Left Ventricle	Brachial Artery	
Normal Ventricular Complex										
W. A. T.	45	2.3	(3)	22–25/2–5	25–28/8–11 (16)	(12)	(20)	...	119–131/65–74 (93)	376
H. S.	50	1.9	(6)	24–28/3–5	27–29/15–17 (20)	...	(10)	120–124/11–13	128–132/98–102 (108)	457
F. R.	22	1.9	(4)	35–40/4–6	38–42/10–20 (23)	(15)	...	...	110–132/60–72 (86)	511
H. H.	29	1.6	(0)	52–58/4–6	50–55/18–22 (33)	(25)	...	...	116–124/58–62 (75)	996
E. M. L.	26	1.4	(2)	44–50/0–2	46–52/28–30 (38)	(21)	...	...	95–130/60–90 (102)	1,332
U. J.	47	1.3	...	52–58/3–7	54–60/17–23 (38)	(11)	...	...	122–130/58–63 (80)	1,447
B. A.	35	...	...	...	...	...	(20)	...	87–96/60–64 (66)	...
R. B.	24	...	...	...	...	...	(12)	110–112/16–20	118–122/77–79 (96)	...
M. B.	28	...	...	...	...	...	(18)	...	120–150/68–72 (80)	...
H. E.	26	...	...	...	...	...	(8)	144–148/0–2	150–162/70–74 (97)	...
P. F.	33	...	...	...	...	...	(9)	117–125/3–6	130–138/71–77 (96)	...
C. L.	33	...	...	...	...	...	(20)	116–124/6–10	114–150/80–100 (104)	...
L. S.	40	...	...	...	...	...	(33)	...	84–96/73–79 (92)	...
A. Z.	39	...	...	...	...	...	(20)	105–115/6–14	120–140/78–82 (100)	...
C. M.	51	...	...	...	...	...	(18)	124–128/6–10	132–142/63–75 (82)	...
Left Ventricular Hypertrophy										
G. R.	54	2.1	(4)	30–39/0–4	32–38/15–19 (28)	(21)	...	...	174–180/100–106 (132)	508
R. L.	30	1.6	(4)	32–40/2–5	30–40/10–18 (20)	(10)	...	...	108–124/50–70 (84)	639
W. B.	24	1.8	(2)	36–40/0–1	36–44/15–17 (23)	(10)	...	...	126–144/50–60 (98)	634
K. D.	30	1.4	(6)	30–40/2–5	32–40/15–18 (28)	(16)	...	...	...	1,060
A. DeL.	42	1.1	(4)	45–64/2–4	50–60/17–20 (33)	(27)	...	...	100–108/68–78 (79)	1,360
F. S.	32	2.2	(12)	55–76/4–10	55–78/36–40 (48)	(25)	...	...	...	1,036
J. S.	42	...	(8)	60–68/0–4	56–66/35–40 (45)	...	...	...	125–150/70–85 (90)	...
W. T.	30	...	(10)	18–22/6–10	17–22/8–12 (14)	...	(19)	88–94/8–12	100–108/56–64 (84)	...
J. C.	36	...	...	...	...	...	(12)	...	114–126/57–64 (90)	...
Combined Ventricular Hypertrophy										
D. R.	15	2.4	(0)	20–26/0–4	17–26/4–10 (11)	(3)	...	...	100–108/40–56 (76)	700
Incomplete Right Bundle Branch Block										
N. Y.	39	...	(10)	30–34/2–6	27–34/15–20 (22)	...	(16)	100–108/18–22	115–140/70–80 (86)	...
C. Z.	50	...	...	...	...	...	(24)	...	145–155/98–102 (115)	...
Right Ventricular Hypertrophy										
A. C.	29	1.8	(0)	62–80/0–2	70–85/32–48 (45)	(28)	...	...	121–125/65–70 (90)	1,285
P. A.	40	1.6	(8)	...	(48)	(20)	...	...	...	1,411
F. W.	37	1.3	(4)	49–57/0–2	52–58/16–20 (33)	(13)	...	...	84–88/30–32 (55)	1,200
E. B.	20	1.4	(5)	62–72/4–10	62–70/30–40 (52)	...	...	...	120–130/76–80 (98)	1,940

* Figures in parenthesis refer to mean pressures.

of ventricular complex in the electrocardiogram did not bear any relation to the cardiac index. The average cardiac index in the present series was somewhat lower than that of a comparable group of patients with pure mitral stenosis reported on by one of us; in the latter it ranged from 1.1 to 4.8 with an average of 2.2 L./min./M² [*6*]. Low cardiac indices in patients with mitral regurgitation have been observed by others [*7,8*].

The left atrial mean pressure ranged from 8 to 33 mm Hg, with an average of seventeen. It exceeded 10 mm. Hg in 83 per cent of the cases (fifteen of eighteen). There was no significant difference between patients with normal sinus rhythm and those with atrial fibrillation, just as there was none in the various ventricular patterns. A prominent C-V wave was recorded in 94 per cent of the cases.

The "pulmonary venous capillary" (PVC)

pressure ranged from 3 to 28 mm. Hg, with an average of 15. It exceeded 12 mm. Hg in 52 per cent of the cases (seventeen of the patients with normal sinus rhythm and 66 per cent of those with atrial fibrillation). A prominent C-V wave was present in 83 per cent of the tracings. More pronounced deviations from normal pressures and contours were found in the direct left atrial recordings as compared with PVC. This is in agreement with the general opinion that the pulmonary wedge pressure represents only an approximation of the events in the left atrium and is subject to artifacts and technical deficiencies [*9*].

The PVC and left atrial pressure contours have long been favorite objects of analysis in the search for a diagnostic clue to the differentiation of "pure" or almost "pure" mitral regurgitation from "pure" mitral stenosis or mitral stenosis associated with slight regurgitation. We have studied the left atrial tracings for a critical evaluation of the various formulas proposed so far. The results, listed in order of the relative accuracy of the various methods, are as follows: (1) ratio of the rate of y descent to the absolute pressure of the V wave (Ry/V was in excess of the critical value of 2.2 [*10*] in 60 per cent of the measurable cases of the present series); (2) V-C difference of more than 8 mm. Hg [*11*], in 50 per cent; (3) ratio of the V wave to the mean left atrial pressure, V/$\bar{P}$LA, of more than 1.5 [*12*], in 40 per cent; (4) ratio of the rate of y descent to the mean left atrial pressure, Ry/MLAP, exceeding 4 [*7*], in 40 per cent; (5) ratio of the rate of y descent during the first 0.1 second to the left atrial mean pressure in excess of 0.5 [*7*], in 40 per cent; (6) V wave minus left atrial mean pressure, V-$\bar{P}$LA, of more than 10 mm. Hg [*13*], in 30 per cent; (7) ratio of the difference between the pressure at the top of the V wave and that at the beginning of the C wave (Z) to the pressure at the top of the V wave, $\frac{Pv - Pz}{Pv} \times 100$, of more than thirty in patients with normal sinus rhythm and of fifty in those with atrial fibrillation [*14*], in 20 per cent; and (8) ratio of the pressure at the top of the V wave to that at the top of the A wave, V/A, of more than 1.4 [*7*], in none of the patients with normal sinus rhythm of the present series.

The inadequacy of the various formulas is evident. Furthermore, considerable overlapping of results occurs when mitral stenosis and regurgitation are combined [*12,13*]. It seems fair to say that if these formulas are utilized in any diagnostic study, they should be employed only in conjunction with clinical, roentgenographic, electrocardiographic and other hemodynamic data.

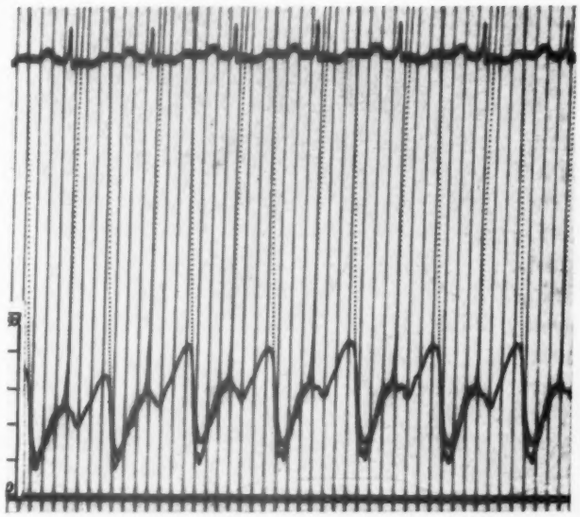

FIG. 3. Tracing of simultaneous left atrial and ventricular pressures in mitral regurgitation, showing reduced X wave, prominent V wave, and no appreciable pressure gradient between left atrium and left ventricle at the time of ventricular filling.

In six of the eighteen patients in whom left heart catheterization was performed alone or in combination with right heart catheterization, the left ventricle could not be entered in spite of prolonged manipulation. In the remaining twelve patients the "wash out" of the catheter from the left ventricle to the left atrium during ventricular systole was a common phenomenon. This experience, of considerable qualitative value, has already been described [*15*].

In these patients the left ventricular end-diastolic pressure was within the upper limits of normal (10 mm. Hg) in all but three cases. Normal or increased pressures similarly have been reported in previous studies [*15–17*].

In six of the twelve patients in whom left atrial and left ventricular pressures were obtained, no left atrial left ventricular filling pressure gradient was noted. (Fig. 3.) In the remaining six, mean gradients and gradients during early, mid- and late-diastole were recorded as follows: 2 (6-1-0), 3 (6-3-0), 4 (8-3-0), 8 (14-8-0), 7 (8-7-6), 13 (11-10-13) mm. Hg. The four patients with gradients limited to early- and mid-diastole showed no evidence of even minimal mitral stenosis at surgery. In one patient (7 mm. Hg) the gradient persisted, although reduced, until

the late phase of ventricular filling. In the only patient of these six with a normal sinus rhythm, a gradient of 13 mm. Hg was recorded, which decreased in mid-diastole and rose again at the time of atrial contraction, giving the appearance of a curve similar to what is observed in mitral stenosis. It is of interest, although possibly coincidental, that in the latter two patients with a gradient persisting until the end of ventricular filling, dynamically significant mitral insufficiency was found to be accompanied by slight anterior commissural fusion at surgery. Transmitral gradients have been reported in severe mitral insufficiency and have been ascribed to "relative stenosis due to the increase in forward flow across the valve as a result of the large regurgitant flow" [*9,15*].

The systolic pressure in the pulmonary artery ranged from 18 to 77 mm. Hg, with an average of 41; the mean pressure varied from 11 to 52 with an average of 28. In patients with normal sinus rhythm the values were, respectively, 18 to 63 mm. Hg with an average of 30, and 11 to 45 mm. Hg with an average of 19. Patients with atrial fibrillation had respective values of 20 to 77 mm. Hg with an average of 48, and 14 to 52 mm. Hg with an average of 30. These values did not vary significantly with the type of ventricular complex in the electrocardiogram except in patients with right ventricular hypertrophy who did show pressure levels in the pulmonary artery significantly higher than the rest of the group. Twenty-two per cent (two of nine) of the patients with normal sinus rhythm had pulmonary hypertension, which was mild in both instances (36 to 60 mm. Hg). Of the patients with atrial fibrillation, 75 per cent (fifteen of twenty) had pulmonary hypertension and this was mild in ten and moderate (61 to 90 mm. Hg) in five.

The total pulmonary resistance ranged from 196 to 1,940 dynes second cm.$^{-5}$, with an average of 813 for the total group. In patients with normal sinus rhythm it ranged from 136 to 610, with an average of 394, the value of 610 dynes second cm.$^{-5}$ being obtained in the only patient with combined ventricular hypertrophy in the electrocardiogram. Four of the patients with atrial fibrillation (and normal ventricular complexes or left ventricular hypertrophy) had values smaller than 610. All patients with right ventricular hypertrophy in the electrocardiogram had a total pulmonary resistance in excess of 1,000 dynes second cm.$^{-5}$ [*18*]. These in regard to pulmonary artery pressure and total pulmonary resistance confirm previous reports [*7,9*].

The right atrial pressure varied from 0 to 12 mm. Hg, with an average of 3.6 for the whole group. In patients with normal sinus rhythm it ranged from minus 2 to 10 mm. Hg with an average of 1; in those with atrial fibrillation, from 0 to 12 mm. Hg with an average of 4.8.

The influence of age upon the several cardiac parameters analyzed in the present series is of interest. The incidence of atrial fibrillation, the left atrial and PVC mean pressures, and the total pulmonary resistance showed an increase with age whereas the cardiac index manifested an opposite trend. It is conceivable that these various derangements are influenced by the age of the patient and the duration of the disease. The heart size and the type of ventricular complex in the electrocardiogram, however, correlated poorly with age, suggesting perhaps that the degree of ventricular damage caused by the underlying rheumatic heart disease played a more important role in affecting these two parameters.

Patients with normal sinus rhythm were, on the average, younger than those with atrial fibrillation (twenty-seven versus thirty-five years). The left atrial and total heart size were appreciably smaller, and the pulmonary artery pressure and total pulmonary resistance were lower. The mean cardiac index was higher and normal ventricular complexes or those indicative of left ventricular hypertrophy were the only patterns seen in the electrocardiogram (with the exception of one patient with combined ventricular hypertrophy). Here again the shorter duration of the disease appears to be the underlying key factor (average period since first attack of rheumatic fever or equivalents: fourteen years in patients with normal sinus rhythm and twenty-three in those with atrial fibrillation).

The cardiac dynamics correlated poorly with the type of ventricular complex except in those cases with right ventricular hypertrophy in the electrocardiogram. The heart size was greater in patients with combined or right ventricular hypertrophy than in those with a normal ventricular complex or left ventricular hypertrophy. Larger hearts were associated with a lower cardiac index and greater total pulmonary resistance. The left atrial mean pressure and total pulmonary resistance in patients with a heart size up to 2 plus were half those with heart size exceeding this value.

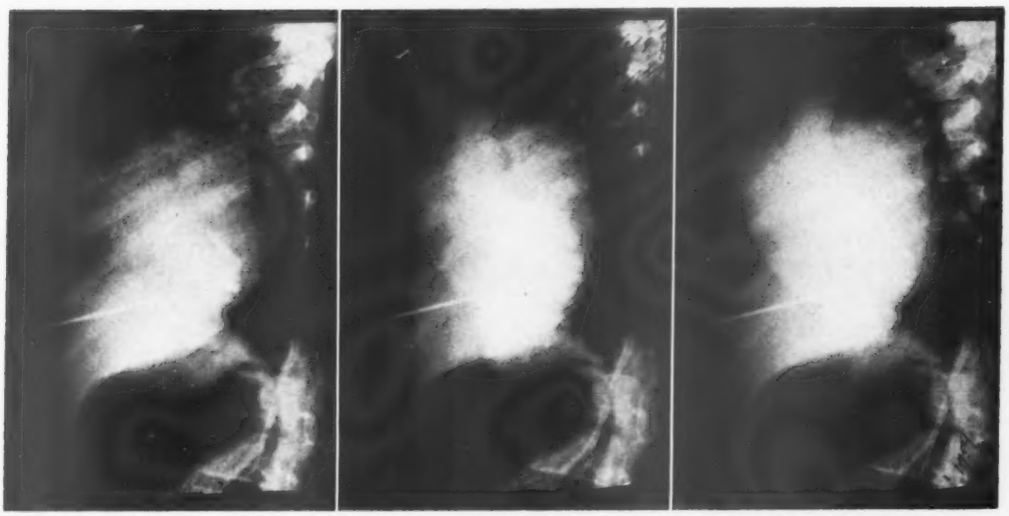

FIG. 4. Cardiac ventriculography. There is marked reflux of contrast material from the left ventricle into the left atrium, indicating significant mitral regurgitation. The left atrium is clearly outlined.

A number of methods for estimating the presence and degree of mitral regurgitation have been devised during the recent years, employing indicator dilution or radioactive substances and utilizing the technic first described by Stewart in 1897 for the measurement of cardiac output. Sites of injection are the left ventricle and/or pulmonary artery, with continuous sampling from the left atrium and/or a systemic artery. The regurgitant volume is usually expressed as a percentage fraction of the forward output, utilizing the concentration curves obtained from left atrium and the systemic artery [*19–23*]. The results have been disappointing, as is to be expected in view of the shortcomings intrinsic to the method. In the first place, the variable size of the left atrium is likely to introduce large errors: small atria tend to exaggerate the degree of insufficiency, because the regurgitant jet undergoes less dilution, large atria have the opposite effect. Secondly, the position of the sampling needle within the left atrium, and its relationship to the regurgitant jet, is an imponderable variable. Consequently, false negatives and overestimation of the degree of regurgitation have been recorded. Our experience with some of these technics also has been disappointing. In our opinion the injection of radiopaque material into the left ventricle with simultaneous serial roentgenography is far superior since the contour of the left atrial chamber is clearly outlined, making it possible to correct for its size, and eliminating the error inherent in sampling from variable sites within the left atrium. (Fig. 4.)

COMMENTS

Regurgitation of part of the ventricular stroke volume back into the left atrium, at the expense of the forward cardiac output during ventricular systole, is the basic qualitative factor initiating the chain of dynamic changes in mitral insufficiency. The anatomic equivalent of this lesion is a persistent communication between left atrium and left ventricle during ventricular systole. Its causes are: (1) reduced leaflet surface (scarring and retraction); (2) increased valve area (dilatation of the mitral ring); (3) lack of approximation and alignment of the valve leaflets during ventricular systole (shortening or rupture of chordae tendineae and/or papillary muscles); or (4) a combination of these causes.

The following qualitative and quantitative factors condition the chain of events in this disease: (1) duration; (2) volume of the regurgitant jet; (3) myocardial efficiency; and (4) intrinsic pulmonary vascular reactivity. The direct relation between the first two factors and the degree of hemodynamic impairment at any given time is evident, as is an inverse relationship between time and volume: smaller regurgitant volumes acting for a longer time are likely to produce results identical or similar to those caused by larger volumes acting for a shorter time (TXV = constant). Less well appreciated

probably is the role which the left ventricular and atrial myocardium play in influencing cardiac dynamics and shaping the course of events. Rheumatic disease, depending on its severity and duration, may cause minimal to marked damage of the ventricular and, to a relatively larger extent, atrial musculature.

A slightly damaged myocardium will maintain virtually unaltered its basic muscular properties of elasticity and contractility. The left atrium, under these circumstances, will offer considerable resistance to the left ventricular regurgitant volume and reduce it a fraction proportional to the resistance offered. The pressure within the atrium will rise significantly during the regurgitant phase (and during the following atrial systole) owing to its high elasticity/volume quotient, without marked changes in volume, and hypertrophy will eventually occur. In our experience, in both dynamically significant mitral stenosis and insufficiency, small atria are much more difficult to penetrate with the needle during catheterization of the left side of the heart than are large atria. When ventricular filling occurs, a somewhat larger than normal mass of blood is forced into the left ventricle, which compensates, during the following ventricular systole, in the volume of the forward stroke for the fraction lost to the left atrium. The left ventricular end-systolic and end-diastolic volumes will be respectively reduced and increased by a fraction inversely proportional to the left atrial resistance; sinus rhythm will persist for a long period, left ventricular function will not be altered to a major extent; the ventricular myocardium, slightly damaged, will be able to cope with its increased work; and effective cardiac output will tend to remain normal. The accentuated phasic pressure of the left atrium, on the other hand, will be transmitted back to the pulmonary capillaries through the pulmonary veins.

When the myocardium is markedly damaged the left atrium, acting as a low resistance chamber, accommodates a sizable regurgitant volume without significant increase of phasic or mean pressures. At the end of the filling phase the left ventricular volume is appreciably increased, being made up of the venous return plus the sizable regurgitant volume. A normal or almost normal cardiac output can be maintained only at the expense of considerable left ventricular end-diastolic dilatation. The left ventricular end-systolic volume may be decreased to a significant extent. The increased volume load of the left ventricle and the damaged ventricular myocardium will thus result in left ventricular hypertrophy and failure. The combination of left atrial fibrosis and stretching of the atrial wall favors the production of atrial fibrillation. The loss of atrial contractility presumably prevents complete emptying of the left atrium into the left ventricle, thus perpetuating left atrial dilatation and reducing cardiac output. This concept seems to be supported by the significantly lower cardiac index in patients with atrial fibrillation than in those with normal sinus rhythm in the present series, even among patients of approximately the same age. The left atrium, at this point, acts as a large buffer chamber, relatively insensitive to volume changes until the limits of its stretching capacity are reached, at which time the pressure increases precipitously. The resistance to flow through the pulmonary circuit is not appreciably increased as long as the left atrial phasic and mean pressures do not rise significantly.

It is obvious that the condition of the ventricular myocardium plays a most important role; if satisfactory, there may be long asymptomatic periods, if poor the manifestations of left ventricular failure supervene.

The intrinsic reactivity of the pulmonary vasculature also plays a role; in addition to backward pressure from the left atrium, accelerating (if marked) or retarding (if slight) the process of right ventricular hypertrophy and eventual failure, through increased resistance to flow in the pulmonary circuit.

SUMMARY

The clinical and physiologic features of sixty-five patients with mitral regurgitation of rheumatic origin were studied.

1. A long asymptomatic period averaging 10.6 years was observed. Contrary to previous reports dyspnea, as well as fatigue, was found to be an early and constant symptom present in over 90 per cent of the patients.

2. In addition to the pansystolic murmur constantly present, a mid-late diastolic murmur was heard in forty-one patients (63 per cent) despite little or no mitral obstruction. A diastolic gallop sound was a very frequent finding.

3. Electrocardiographic evidence of left ventricular hypertrophy was found in only one-third of the patients. A normal ventricular

complex was present in 50 per cent, while right ventricular hypertrophy was observed in 15 per cent of the cases.

4. The typical roentgenographic finding was an enlarged left atrium with a wide sweep of barium esophagram contrasted to the localized posterior displacement seen in pure mitral stenosis.

5. The cardiac index was low in the group with atrial fibrillation and normal in patients with normal sinus rhythm. A large C-V wave (ventricularization) was found in the left atrial (93 per cent of the patients) and pulmonary wedge pressure curves (83 per cent of the patients). A ventricular filling gradient, when present, is confined to early diastole. In the present series, the most reliable method for the qualitative and quantitative estimation of the degree of mitral regurgitation was ventriculography employing injection of radiopaque material into the left ventricle with simultaneous serial roentgenography of the cardiac silhouette.

6. Sixty-four patients were operated upon for correction of the regurgitation. At surgery, the regurgitation was found to be almost invariably posterior. Calcification of the valve was noted in 31 per cent of the patients operated upon. In approximately 12 per cent of the cases Ashoff bodies in various stages of evolution were found in the biopsy specimens of the left atrium.

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Familial Cardiomyopathy*

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The familial aggregation of primary myocardial disease in the absence of Friedreich's ataxia or somatic myopathies is rare. Since Evans' [*1*] description of familial cardiomegaly in 1949 there have been a few reports in the British literature of families so affected [*2–5*]. Sommers' report [*6*] on familial cardiopathy included three siblings at autopsy but the pathologic findings were so dissimilar as to lead the authors to question the operation of a single mechanism. Paulley's report of three affected siblings [*4*], two of whom had detailed postmortem examinations, is thus far the best documented report of a family in whom the criterion of pathologic similarity is adequately fulfilled. Unfortunately, most other reports include only a single detailed necropsy and employ the similarity of clinical course and findings before death in establishing the familial nature of the disorder.

This report will present a sibship in which it is presumed that five members have an identical cardiomyopathy. Two have had autopsies and identical gross and microscopic myocardial pathologic disease was demonstrated. Two have died from cardiac disease without having postmortem examinations, but the clinical information is sufficient to classify one as a presumptive case and the other as a possible case. The remaining sibling is living and is being followed up in this hospital.

CASE REPORTS

Case 1. J. D. T., (Johns Hopkins Hospital No. 767853). This patient, a white male aged twenty-eight, was seen for the first time in the Johns Hopkins Hospital in April 1957 four months prior to his death. Ten years previously he had been told he had a "skip in the heart" but was pronounced fit. He had no symptomatology referable to the cardiovascular system until twenty-two months before his death. From that time on he had dyspnea and palpitations on exertion associated with an epigastric pressure sensation that radiated to his flanks. These symptoms increased in frequency and severity and began to appear even at rest late in the course of his illness without apparent precipitating factors.

On physical examination the patient was well nourished and well developed and did not appear ill. Pulse rate was 96 per minute with a regular rhythm and the blood pressure in the arm was 100/70 mm. Hg. Pertinent physical findings were limited to the cardiac examination; the apex beat was barely palpable in the fourth left intercostal space just beyond the mid-clavicular line, the second sound was accentuated over the entire precordium but was loudest and widely split in the pulmonic area; a soft systolic murmur in the pulmonic area was intermittently heard; there were no adventitious sounds. There was no distention of the neck vein, hepatomegaly or peripheral edema. Fluoroscopy of the chest revealed generalized cardiac enlargement, with the left atrium and ventricle most prominent; the area of the pulmonary conus was normal as was the pulmonary vasculature. (Fig. 1.) The electrocardiogram was interpreted as showing right axis deviation, right ventricular hypertrophy and right bundle branch block. The P waves were broad and notched. (Fig. 2.)

Numerous studies were carried out on three elective admissions over the next two months. Results of the serological test for syphilis were negative; protein bound-iodine was 6.6 μg. per cent; serum electrolytes and proteins were within normal limits; no lupus erythematosus cells were seen in two preparations. The serum cholesterol was 266 mg. per cent. The circulation time (arm-to-tongue, Decholin®) was thirty-five seconds and the venous pressure was 105 mm. of water. Vim-Silverman needle biopsy of the liver yielded normal liver tissue. The serum non-protein nitrogen was 33 mg. per cent and the fasting blood sugar 92 mg. per cent. The urine was clear.

Right and left heart catheterization was performed to rule out septal defects and obstructive lesions of the left side of the heart. Right ventricular, pulmonary artery and pulmonary wedge pressures were elevated. Diastolic pressure was elevated in the left atrium and left ventricle without any gradient across the mitral

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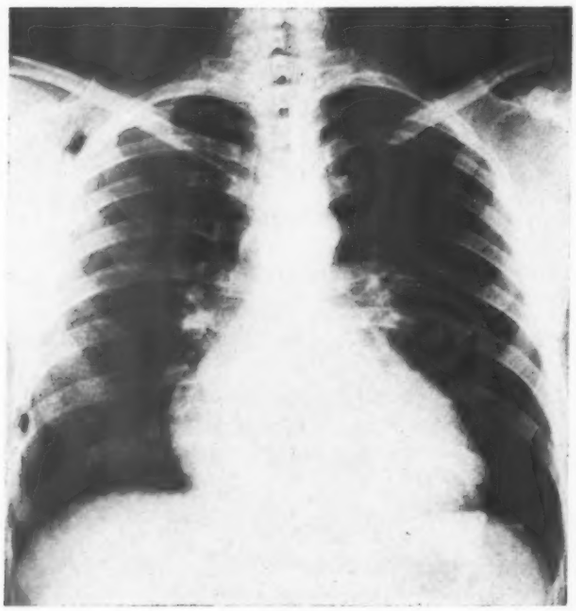

FIG. 1. Chest film of Case I.

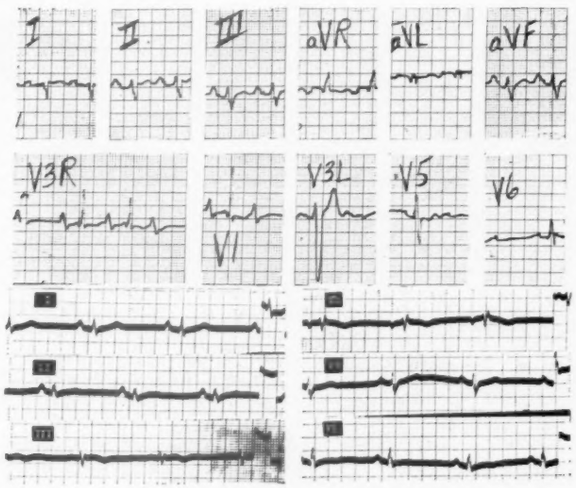

FIG. 2. Electrocardiogram obtained for two patients (Case I above and II below). Digitalis had been administered in Case I. In Case II (pericardial effusion) no digitalis had been administered.

valve. There was no evidence of a shunt and the tracings in the ventricles were not suggestive of restrictive disease. A diagnosis of idiopathic myocarditis was made.

The patient had a reasonably stable course until ten days prior to death. At that time he had the onset of throbbing pain in the right flank. He went to his local physician and was told that he had blood in his urine. Because of persistence of this pain he presented at this hospital three days later. On examination his heart sounds were poor and he had exquisite right costovertebral angle tenderness. His electrocardiogram showed large notched P waves, greatly prolonged ventricular conduction time and runs of 2:1 auricular-ventricular block and Wenckebach periods with 3:2 block. A diagnosis of progressive myocardial disease and right renal infarction secondary to embolization was made and he was admitted. One day later he had pain in the right upper quadrant of the abdomen and rebound tenderness; it was decided that he should be explored to rule out a surgically treatable acute abdomen. Exploration revealed a large infarct of the upper pole of the right kidney. Prior to operation no red cells were seen in many specimens of urine and an intravenous pyelogram was normal.

During the procedure he became markedly cyanotic and his condition rapidly deteriorated thereafter. Two days later he had a sudden burst of tachycardia and tachypnea followed by hemoptysis suggesting pulmonary embolization. He died suddenly the next day.

At autopsy, there was no evidence of excess fluid in the pleural cavities, but 150 ml. of amber fluid was noted in the pericardial cavity with no adhesions present. The heart weighed 550 gm. and was symmetrically enlarged due to dilatation of all chambers and hypertrophy of both atria. The valves and chordae were thin and delicate but examination of the endocardium revealed thickening of the wall of the left atrium 1 cm. above the base of the aortic leaflet of the mitral valve and patchy thickening of the endocardium of the trabeculae carnae of the left ventricle. A 3 cm. gray thrombus was loosely adherent to the endocardium at the apex of the left ventricle. The myocardium was firm and reddish brown with slight focal gray discoloration throughout. The coronary ostia, arteries and veins, and coronary sinus were widely patent. There were focal areas of peripheral induration and dark red discoloration in both lower lobes of the lungs. No areas of pulmonary infarction could be seen. The liver showed evidence of slight central venous pallor. There were fresh areas of infarction in both kidneys, the largest at the upper pole

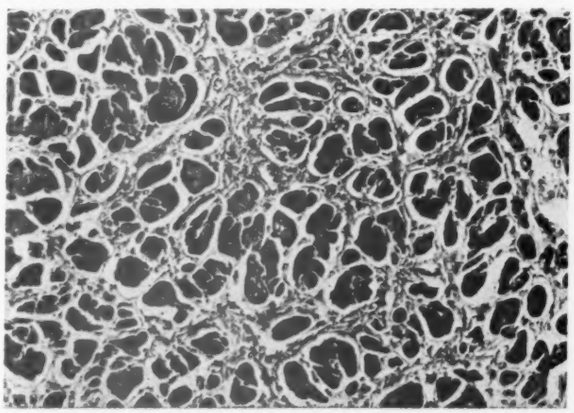

FIG. 3. Case I. Lacelike, vascularized interstitial scarring. Original magnification × 130.

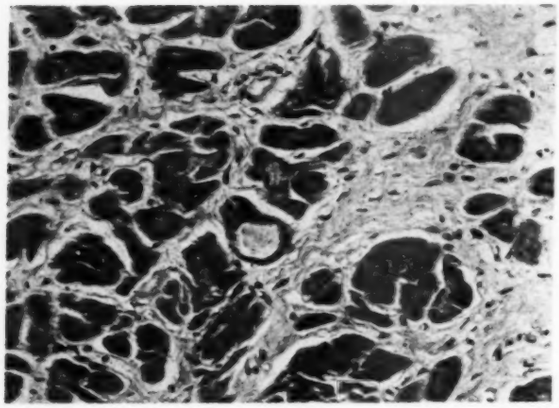

FIG. 4. Case 1. Hyaline plaque distending myocardial fiber with adjacent interstitial scarring. Original magnification × 245.

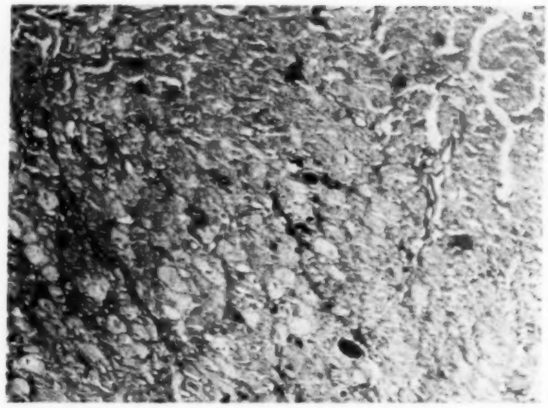

FIG. 5. Case 1. Staining of hyaline plaques in myocardium by periodic acid-Schiff reaction. Original magnification × 105.

of the right kidney. The abdominal and pelvic organs and the cranial contents were normal.

Microscopic sections of the myocardium revealed a diffuse, finger-like interstitial network of scarring with a prominent vascular proliferation producing apparent separation of muscle fibers. (Fig. 3.) In these areas evidence of myocardial degeneration consisting of vacuolization with disintegration and dissolution of the fibers was seen. More prominent areas of scarring were present, consisting of dense hyaline and collagenous replacement of the myocardium. (Fig. 4.) In phosphotungstic acid-hematoxylin stains cross-striations were noted to be intact until almost complete replacement of the fiber by the hyaline substance occurred. Fragments of this material were occasionally present as plaques isolated in dense collagenous tissue. This material was not metachromatic with cresyl violet or toluidine blue but was reactive to periodic acid-Schiff (Fig. 5), Bauer, Cassella and Gridley stains both before and after diastase digestion. The material failed to take the usual fat stains. A moderate amount of lipofuscin pigment was present in the myocardial fibers but no excess glycogen was noted.

Prominent hypertrophy of many myocardial fibers with numerous bizarre nuclei was seen. In the left atrium there was endocardial thickening over a small area consisting of swelling of loose collagenous tissue fibers with fibroblastic proliferation. Peripheral organization of an early thrombus adherent to the endocardial surface of the left ventricle was noted. The major coronary arteries were widely patent, only one showing a focus of fatty macrophages in the intima; the smaller arterial channels in many areas had a markedly narrowed lumen as a result of extensive increase in smooth muscle and collagenous tissue of the media, and many of these showed prominent stenosis of the lumen. (Fig. 6.) No inflammatory cells were noted and no localized perivascular fibrosis was seen.

In several sections of the lungs there was prominent necrosis of peripherally disposed alveolar septums with hemosiderin containing macrophages in alveoli and fresh thrombus material in small pulmonary arteries. There was marked congestion of the central veins and sinusoids of the liver, congestion of splenic pulp and atrophy of peripheral acinar cells of pancreatic lobules. Organizing thrombi were present in intralobular renal arteries, with extensive fresh infarction of the kidneys.

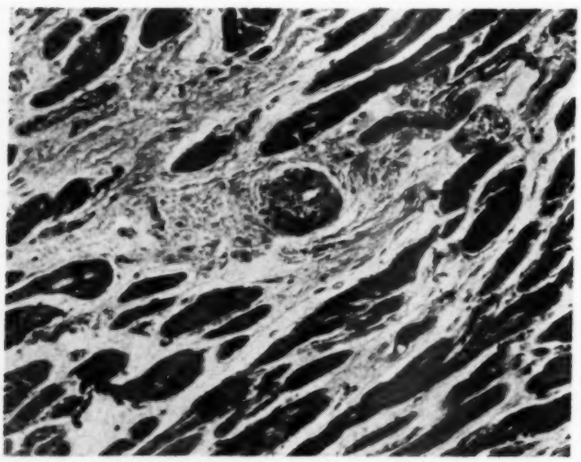

FIG. 6. Case 1. Prominent hypertrophy of media of small artery producing luminal narrowing. Original magnification × 170.

Comments. This young man apparently had a rapid progression of his cardiac disease, with death coming twenty-two months after the onset of significant symptoms. Whether the "skip in the heart" ten years previously was a significant arrhythmia or a gallop rhythm cannot be known.

Digitalization did not affect his symptomatology. Although embolization and exploration probably hastened his demise, the electrocardiographic deterioration probably was an omen of impending cardiac catastrophe. Dr. Arnold Rich commented that " . . . there is nothing to suggest an old or fresh rheumatic process, and no inflammatory residue or any other process leading to scarring of the myocardium."

It was known that the patient's sister had been treated for pericardial effusion in this hospital and had died in another hospital after partial pericardiectomy. Sections of her heart obtained at autopsy revealed myocardial scarring and were available for comparison at the time of her brother's death.

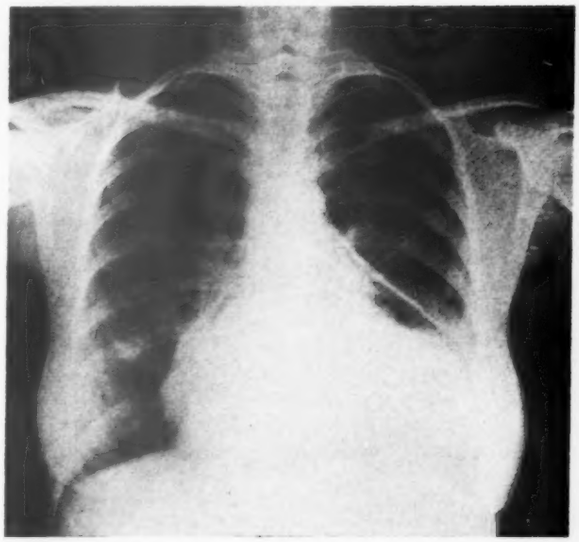

FIG. 7. Roentgenogram of chest in Case II showing induced pneumopericardium following pericardial tap. The haziness in the right lung is due to residual contrast media following bronchography.

CASE II. N. W., (Johns Hopkins Hospital No. 463862). This patient, a thirty-nine year old sister of Case I, was first seen in this hospital at the age of thirty-seven with complaints of shortness of breath and pain in the left side of her chest of at least twelve months' duration. She had had recurrent bronchitis in childhood and a persistent productive cough since then. She had chronic sinusitis and two episodes of lobar pneumonia during her adult life. On several occasions she noticed painless gross hematuria which was never adequately explained. Five years prior to her admission she had a skin rash followed by polyarthritis and was told that she had rheumatic fever. Six months later a routine roentgenogram of the chest was taken and her heart was said to be enlarged. During the next few years she had the insidious onset of exertional dyspnea and then ankle edema and paroxysmal nocturnal dyspnea developed.

On her initial admission no apex beat was palpable and the left border of cardiac dullness extended almost to the anterior axillary line. The liver edge was four fingerbreadths below the right costal margin. There was no peripheral edema. Electrocardiogram showed sinus bradycardia, low amplitude and low T waves. Pericardial paracentesis yielded 600 ml. of clear fluid with a specific gravity of 1.016. Microscopic examination and diverse cultures were unrevealing.

During the following year she had numerous pericardial taps (Fig. 7) and extensive diagnostic investigation without any cause of her disease becoming apparent. When last seen in this hospital she continued to have a large pericardial effusion, hepatomegaly and no peripheral edema. Her blood pressure on all occasions was low normal in the range of 105/70 mm. Hg. Her electrocardiogram showed low voltage, T wave changes and some prolongation of the P-R interval and the QRS duration. (Fig. 2.) No arrhythmias or gross conduction defects appeared.

During the final fifteen months of her life she was followed up in another hospital and had several episodes of a "shock like picture" with hypotension and cyanosis. Her pericardial effusion persisted and she had repeated withdrawals of fluid. Because it was thought her pericardial disease caused her to be an invalid a partial pericardiectomy was performed. At operation the heart action seemed to improve after the pericardium was removed from the left two-thirds of the heart. Two days later she suddenly became hypotensive and died in a few hours.

At autopsy, there was a left thoracotomy incision with a drainage site still patent. Dense fibrous pleural adhesions obliterated the pleural cavities bilaterally. The left half of the pericardium was surgically absent. A focal area of dense adhesions was present in the region of the pulmonary conus. The heart weighed 460 gm. and the epicardial surface was roughened, with many fibrous tags present. The right auricle was slightly dilated and the left ventricular myocardium, although normal in appearance, seemed somewhat thinned. The valves were normal and the coronary arteries had delicate walls and were patent throughout. There were several areas of dark discoloration at the periphery of the left lower lobe of the lungs. The liver weighed 1,450 gm., had a nodular surface and a pronounced nutmeg appearance on section. The other abdominal organs were normal. No abnormalities were noted in the cranial contents.

Microscopic sections of the heart revealed thickening of the epicardial fat with collagenous and vascular ingrowth and lymphocytic collections near the epicardial surface. There was a diffuse fibrosis of the myocardium with areas of vascularized connective tissue separating muscle fibers. (Fig. 8.) Individual muscle fibers showed hypertrophy with bizarre nuclei, some showing pyknosis. Vacuolar degeneration of

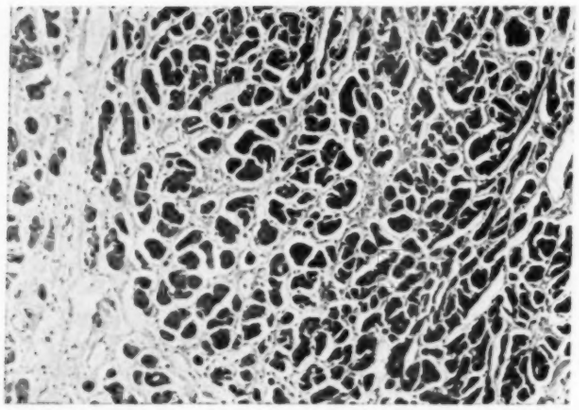

FIG. 8. Case II. Similar scarring of interstitial tissue as in Figure. Original magnification 1. × 120.

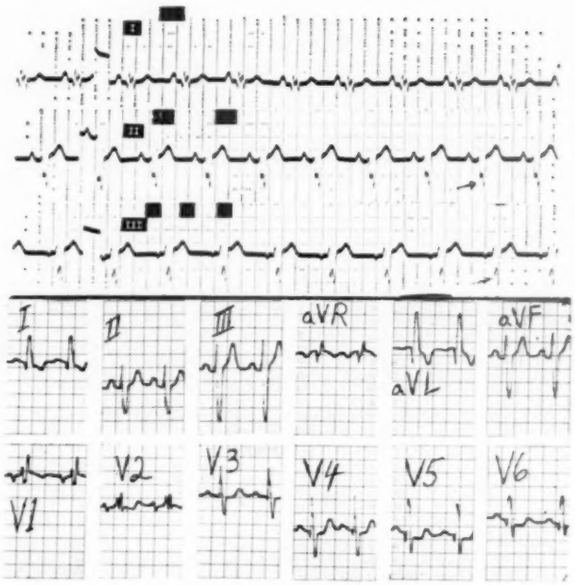

FIG. 9. Electrocardiograms obtained for two patients (Cases IV above and V below). In both cases no digitalis was administered.

muscle fibers was noted and a non-metachromatic, periodic acid-Schiff reactive material that was diastase-resistant was present in many fibers. No significant cellular infiltration of the myocardium was noted and the endocardium was not thickened. The major coronary arteries showed intimal proliferation in several foci but no encroachment on the lumen. The small arteries and arterioles showed marked medial thickening composed of smooth muscle proliferation and an increase in collagenous tissue with distinct luminal narrowing. Moderate quantities of lipofuscin pigment were present in myocardial fibers but no excess glycogen was seen.

In several sections of the lungs there was slight thickening of the alveolar septums by fibrosis and in a few areas hemosiderin pigment in macrophages was noted. In the left lung some of the small arteries showed intimal proliferation and medial thickening. There was distortion of the lobular pattern of the liver with tongues of collagenous tissue radiating from dilated central veins. Moderate fatty infiltration of the pancreas was present.

Comments. This patient's disease was thought to be mainly pericardial, and the finding of extensive myocardial disease was unexpected. The cause of the massive effusion is still unexplained, although it is possible that it might have been a manifestation of cardiac failure. There was no evidence of active pericardial inflammation at necropsy that could not be explained by the surgical procedure. The microscopic pattern of the myocardium was identical with that of Case I. Information was obtained on two other deceased siblings.

CASE III. O. D., a female sibling, died at the age of forty-eight of cardiac disease. For several years prior to death she had mild congestive failure with hepatomegaly and abdominal distention but without peripheral edema. On her last admission to a local hospital physical examination showed a heart "somewhat enlarged," a slight systolic murmur and a blood pressure of 110/80 mm. Hg. The pulse was said to be irregular, suggesting atrial fibrillation. The liver was palpable and there was slight general abdominal distention. The red blood count was 5.4 million per cu. mm. and the urine was clear except for transient albuminuria. Despite digitalization and supportive measures the patient died eleven days after admission. No postmortem examination was obtained. The patient died in 1950. Unfortunately no roentgenograms of the chest or electrocardiograms are available.

CASE IV. E. T., another male sibling, was admitted to a North Carolina hospital in 1936 at the age of twenty-three with a diagnosis of acute appendicitis. Operation the next day confirmed the diagnosis. An electrocardiogram revealed a P-R interval of 0.20 and a gross intraventricular conduction defect. (Fig. 9.) On physical examination the point of maximal cardiac impulse was in the sixth left intercostal space in the anterior axillary line. A questionable low pitched murmur was heard at the apex. There was no edema. He was discharged fourteen days after admission and died at home several weeks later of unknown cause. No autopsy was performed. There was no history of rheumatic fever.

Comments. Case III is poorly documented and one cannot be certain of the nature of the cardiac disease. The grossly abnormal electrocardiogram in Case IV is very unlikely to have been the result

FIG. 10. Chest film of Case V.

of rheumatic disease, although possible in precocious coronary artery disease. However, in this family setting it is most probably the result of primary myocardial disease.

CASE V. O. D., (Johns Hopkins Hospital No. 790437). This patient, a female thirty-nine years of age, was seen for the first time in November 1957 when the other members of the sibship were examined for heart disease. For the past six or seven years she had had dyspnea on exertion and several times experienced an acute sensation of abdominal fullness. She has minimal orthopnea and has had occasional paroxysms of nocturnal dyspnea. She had had several syncopal attacks, the most recent being followed by localized pleural pain.

Physical examination revealed a well developed, slightly obese white woman in no distress. Blood pressure in the arm was 116/84 mm. Hg with a pulse rate of 92 per minute. The arterial pulsations were normal in all extremities. The lungs were clear. The point of maximal impulse was halfway between the mid-clavicular and anterior axillary lines in the sixth left interspace. The second pulmonic sound was accentuated and split. A short low pitched mid-systolic sound was heard at the apex in the sitting position. There was no venous hypertension, no hepatomegaly and no edema. Fluoroscopic examination revealed a heart with moderate diffuse cardiomegaly. (Fig. 10.) All chambers appeared enlarged except that the left atrium did not definitely displace the barium filled esophagus. The electrocardiogram showed left axis deviation, P waves suggestive of combined atrial hypertrophy, and left ventricular conduction disturbance. (Fig. 9.) Circulation time was twenty-four seconds and the venous pressure 80 mm. of saline. Numerous laboratory tests were within normal limits including serum electrolytes and proteins, lupus preparations, protein-bound iodine and serological tests for syphilis.

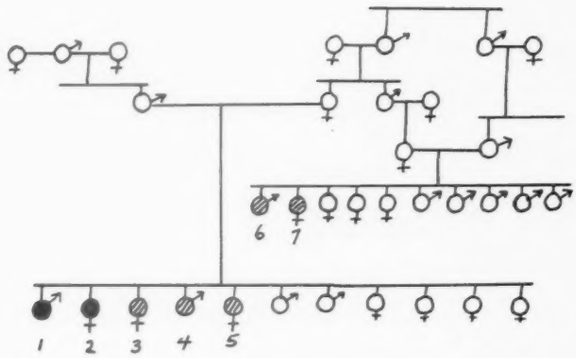

FIG. 11. Pedigree of family. Numbers correspond to case numbers in text. Closed circles indicate proved cases, hatched circles represent presumed cases and open circles unaffected cases.

During the ten months that she has been followed up by one of us she has deteriorated only slightly, with further reduction in exercise tolerance. First degree heart block has appeared in the electrocardiogram and a sizable R′ deflection has appeared in V_1. The heart size on roentgenograms of the chest has not increased. Syncopal attacks have increased in frequency and one attack has been documented as a run of rapid supraventricular tachycardia.

Comments. This patient almost certainly has primary myocardial disease. There are no significant murmurs, moderate cardiomegaly is present, and gross conduction defects are demonstrable on the electrocardiogram.

Additional Family History (*Fig. 11*). The mother, age seventy-three, of this sibship, two male siblings, ages thirty-four and thirty-seven, and three female siblings, ages fifty, fifty-two and fifty-three, have been examined, fluoroscoped and have had electrocardiograms recorded in this hospital; they have shown no evidence of serious heart disease. The father is living at age seventy-five. An additional female sibling was not examined but is said to be in good health.

None of the patients examined gave a history of diphtheria or rheumatic fever, or could they remember that the deceased members of the family had such illnesses. There was no evidence from the case histories or physical examinations to suggest any of the myopathies or Friedreich's ataxia. The family denies early death from heart disease in their ancestors and relations except those mentioned.

A consanguineous mating between cousins of the

family has produced ten children, two of whom died in their twenties. Their histories are of interest, although one cannot with certainty maintain the identity of the disease processes in the two sibships.

CASE VI. Ten years prior to death at the age of twenty-seven La. B. was rejected for the armed services for an unknown reason. Five years later he began to have exertional dyspnea. Two months prior to death he had peripheral edema and joint pain and was thought to have rheumatic fever. He had no prior history of the manifestations of rheumatic fever. On examination the pulse was irregular and the blood pressure 120/80 mm. Hg. On admission to the hospital he had cyanosis and was acutely ill. He had rales throughout the chest. The heart was enlarged to the right and left, with the point of maximal impulse near the anterior axillary line. P_2 was louder than A_2; no murmurs were heard. The liver was 11 cm. below the right costal margin. There was slight sacral edema. Hematologic values were within the normal ranges with normal indices, making the possibility of a long-standing shunting lesion as the cause of the cyanosis extremely unlikely. Roentgenograms of the chest showed cardiomegaly and a right pleural effusion. Electrocardiograms showed varying rhythms: atrial fibrillation, sinus and nodal tachycardia. There was left axis deviation and a pattern of left bundle branch block was seen only during nodal tachycardia. (The records were not available for review.) The patient had many episodes of deep cyanosis, dyspnea and profuse perspiration. He died during one of these episodes on the twenty-fifth hospital day. No autopsy was performed.

CASE VII. LO. B., the sister of Case VI, had a history going back several years of dyspnea on exertion prior to her death in her twenties. The family believes she had "attacks" similar to her brother's but know no specific details. She died suddenly one day after admission to hospital. No other information is available.

COMMENTS

William Evans [*1*] introduced the term "familial cardiomegaly" in 1949 to describe the familial aggregation of unexplained cardiac enlargement in adults, and described two families. Autopsy was performed in a single member of each family and there was much interstitial myocardial fibrosis with marked hypertrophy of the remaining muscle fibers. Glycogen deposits in abnormal amounts were described in cardiac and skeletal muscle. Gaunt and Lecutier [*2*] and Campbell and Turner-Warwick [*3*] accepted the designation and added further instances of families presumed to have the same disease. In none of their families was more than one member studied in detail at postmortem. They disagreed regarding the finding of abnormal amounts of glycogen in the myocardium. Paulley et al. [*4*] reported on a family with three affected members, a mother and her two children. The microscopic findings of the siblings were described in detail. One showed fine interstitial fibrosis with some areas of gross fibrosis, the other diffuse areas of dense fibrosis. The family described by Daves [*5*] included a single patient in whom marked myocardial fibrosis showed at autopsy. Other reports of families in which more then one member was autopsied reported dissimilar pathologic data [*6,7*]. Brigden [*8*] added another instance in reviewing the non-coronary cardiomyopathies, but little detail is given.

Until such time as a definite cause can be assigned we believe that primary, isolated myocardial disease with intact coronary arterial supply, resulting in diffuse fibrosis and having familial aggregation should be designated "familial cardiomyopathy" rather than the less specific "cardiomegaly."

Cause. The cause of the myocardial disease in these cases is unknown. Isolated myocardial disease without vascular lesions in adults is still termed "idiopathic." Late death from the residua of diphtheritic myocarditis is uncommon [*9*] but not unknown [*10*], but there is no evidence for this possibility in these cases. There is no evidence that the acute (Fiedler) myocarditis of infancy and early childhood cause permanent myocardial disease resulting in cardiac malfunction in adult life. There are reports of the myocardial disease associated with Friedreich's ataxia [*11*] and pseudohypertrophic muscular dystrophy [*12*] possibly occurring in members of an affected family without the neurologic manifestations, but there has been no evidence to support this possibility in the family reported on herein or recorded in previous reports.

Paulley suggests that the familial aggregation of these cases is the result of common infection with toxoplasma. The evidence is scant and the arguments against this viewpoint, as detailed by Gaunt and Lecutier, are sound. The inconstant finding of abnormal amounts of glycogen in the myocardium makes it unlikely that this disorder is a variant of a glycogen storage disease.

Although the incidence of progressive unex-

plained myocardial disease in adults is not exactly known, it is low [*20*], and the occurrence of more than two cases in a sibship is more likely the result of related mechanisms than a chance occurrence. Although the operation of a common environmental causation cannot be absolutely excluded, there is nothing to suggest this possibility in the family we have studied. There is no history of common illness except the heart disease and this had its onset, at least clinically, many years after the affected persons had moved to different localities. We agree with most previous authors that the most likely cause is genetic and believe that this is an abiotrophic process and an entity *sui generis*.

An analogous isolated myopathy with familial aggregation is ocular myopathy [*12*]. Progressive dystrophy of the external ocular muscles can occur accompanying myopathic changes in other muscles, but there are instances when it is restricted to the ocular muscles and appears in several members of a family. The cause is unknown and although it exhibits analogous manifestations it has not been reported as an accompaniment of cardiomyopathy.

In the absence of satisfactory documentation of the cases in the related sibship it is impossible to assign a definite mode of inheritance. If those cases were indeed instances of the disorder in question the new appearance of a phenotype in the children of a consanguineous mating would strongly suggest a recessive character. Indeed, the family under primary consideration originates from an area where there is a high incidence of intermarriage and the parents may be more closely related than known. A dominant gene with incomplete penetrance could produce affected children in unaffected parents, and only the appearance of the characteristic in the next generation would make this probable. The same would be true for a newly mutant dominant. This has not happened to the best of our knowledge, but we have not had the opportunity to study this generation exhaustively. The evidence available suggests a recessive genetic inheritance in this family. This conclusion disagrees with those of other authors, but it is entirely possible that the mode of transmission varies from family to family.

Pathology. The similarity in the microscopic appearance of the myocardium in the two members of the family reported on herein indicates a similar pathologic process. No evidence for an infectious agent such as toxoplasmosis or sarcosporidiosis is apparent since no organisms were visualized and inflammatory cells were absent from all areas of the myocardium; yet, degeneration of myocardial fibers was in evidence throughout all sections. No stigmata commonly associated with the collagen vascular disorders were noted and no evidence of fibroelastosis was apparent. The lesions described as diagnostic of "cardiovascular collagenosis" [*14*] are absent from these patients.

The question as to whether the myocardial scarring is the result of vascular insufficiency or of an inherent metabolic defect must be considered. Despite the presence of fresh endocardial thrombus material in the left ventricle in Case 1, no thrombotic occlusion of cardiac vascular channels was present. Atheromatous involvement of the intima was evident to only a minimal degree and was consistent with the ages of the patients. The lumina were not compromised. However, in both small arteries and arterioles there was present a prominent proliferation of the smooth muscle fibers of the media with increase in interstitial collagenous material. In areas this process produced marked stenosis of arteriolar lumina. Although a causal relationship with the narrowing of the arteriolar channels producing myocardial damage and subsequent diffuse fibrosis might be invoked, this vascular narrowing is occasionally seen in areas of healed myocardial infarcts in hearts which are the seat of severe major coronary artery disease. Rarely, however, is the process as extensive as in our cases.

That the underlying disease process in these cases of familial cardiomyopathy is inherently the result of a metabolic disturbance is suggested by the presence of abundant, non-metachromatic, diastase-resistant polysaccharide in many muscle fibers exhibiting the identical histochemical reactivity as that seen in myxedematous hearts [*18,19*]. The material previously described in "mucoid" or "basophilic" degeneration of the heart is seen most frequently in an older age group, and then rarely in this amount [*15,19*]. It apparently has no relation to the vascular integrity of the heart since it is not increased in cases of coronary artery disease. It may represent the result of an altered metabolism of myocardial fibers injurious to their function, for in many areas myocardial fibers have undergone complete degeneration, with the basophilic hyaline material remaining entrapped in dense collagenous scars. The degenerative process is

not constantly related spatially to the deposition of this "mucoid" material, and in many areas no relationship whatever exists. The presence of a mucopolysaccharide substance in smooth muscle fibers has been described in cases of myxedema [*16,19*]. No such material was noted in our cases. No vitamin deficiency disease, including that of vitamin E [*19*], has to our knowledge been known to produce a pathologic picture similar to that in our cases. Thus it is impossible to define pathologically the cause of the myocardial changes except to state that no evidence for an infectious agent is present.

Clinical Features. Apparently symptomatology can be quite minimal until near terminal phases of the disease. Even then the symptoms may be bizarre and suggest a non-cardiac basis for the complaints. Episodes of restlessness, syncope, palpitations, giddiness and lassitude appear to be common. Dyspnea may appear without constant relation to exertion. When one patient (Case I) was first seen it was thought that his symptoms were more likely a result of autonomic instability than cardiac disease, until an electrocardiogram was taken. Clinically apparent congestive failure is not an early manifestation. In Case I there was an elevated left ventricular end diastolic, left atrial and pulmonary artery pressures at a time when there was no clinical evidence of failure. Fluoroscopic examination usually reveals cardiomegaly without preferential chamber enlargement and poor pulsations. The apex beat is usually weak to palpation. Murmurs are inconspicuous and those present are probably related to the filling and emptying of dilated ventricular chambers. The second sound may be split, particularly in the pulmonic area, in the presence of gross conduction disturbances. In the electrocardiogram gross conduction defects and arrhythmias are common. Increased voltage has been seen but is not a frequent finding.

Long term prognosis is poor but there is not enough information to allow a short term prognostication in an individual case. The course may be rapidly progressive once major symptoms have appeared.

Treatment is that of congestive failure, if present, and of the several arrythmias. Steroid therapy was considered in Cases I and V but rejected. The absence of any evidence of active myocarditis in the pathologic material makes it unlikely that steroids would affect the inexorable progress of the disease.

SUMMARY

A sibship is reported on of which five members presumably have an identical cardiomyopathy. Pathologic changes in the myocardium of two members of this family consisted of diffuse, finger-like scarring of interstitial tissue with areas of broader scar formation, marked medial hypertrophy of small arterial channels with moderate luminal narrowing, and an abundant deposition in myocardial fibers of a non-metachromatic polysaccharide substance.

Previously reported cases of familial aggregation of obscure myocardial disease are reviewed.

The evidence available suggests that the disorder is a heritable abiotrophic process resulting in a metabolic lesion of the myocardium.

Acknowledgments: We are indebted to Dr. James A. Smith of the U. S. Public Health Service Hospital, Baltimore, Maryland for permission to present the pathologic findings in Case II of this report; Drs. Arnold R. Rich and Helen B. Taussig for helpful review of the manuscript; and Mrs. Laverne Rogers for technical assistance.

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The Coronary Blood Flow as a Critical Determinant of Cardiac Performance and Cardiac Size*

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STARLING'S "Law of the Heart," which relates the strength of contraction directly to diastolic size, is widely held to express the primary mechanism by which *in vivo* performance of the heart is regulated [*1–3*]. Yet it has been demonstrated repeatedly that stroke output or stroke work and cardiac size may vary both independently and inversely under normal physiological conditions [*4–6*]. Although the Frank-Starling [*7,8*] relationship is unquestionably a basic property of muscle, it is conditional to an unchanging metabolic state [*9*]. Since it is unlikely that important changes in cardiac performance ever occur in the intact animal without a concomitant or closely associated change in cardiac metabolism, there is considerable doubt as to the primacy [*6,10*] or indeed even applicability [*11*] of Starling's law to the regulation of the *in vivo* mammalian heart. Failure of the Starling concept to explain the observed data clearly invites consideration of more comprehensive regulatory mechanisms [*4,6,10,11*].

Viewing the heart as a functioning organ with metabolic requirements that apparently vary commensurately with its work load has prompted inquiry into the influence of its metabolism upon both its working capacity and its size. Because cardiac metabolism is so fundamentally influenced by the coronary circulation, the myocardial blood supply has been investigated to define its role as a possible primary regulating and limiting factor of cardiac performance.

It has been frequently observed that direct restriction of coronary blood flow will decrease the contractile capabilities of the heart [*12–17*]. We have employed graded pulmonary artery constriction to limit the coronary circulation (indirectly) and venoarterial shunting [*18*] to augment coronary circulation (indirectly). In this way it was possible to study the extent to which mechanical stress and coronary circulation may act as variables affecting (1) the entry into and emergence from experimental heart failure, and (2) the determination of heart size.

Quantitative data were sought that not only might relate coronary circulation to cardiac contractile capacity but in addition elucidate its possible role as a fundamental and independent determinant of heart size. If heart size can be determined by metabolic factors independently of the work load, there would be some question as to the validity of many of the conclusions based upon the Starling hypothesis in which the coronary blood flow specifically, and myocardial metabolism generally, were not clearly controlled.

METHODS

The studies were made on open chest mongrel dogs varying in weight from 12 to 24 kg. The animals were anesthetized with sodium pentobarbital, 30 mg./kg., with supplementary doses when required. Intermittent positive pressure respiration with room air was administered through a tracheal cannula by means of a motor driven respirator. Clotting was prevented by the administration of heparin. Bilateral groin incisions were made and both femoral arteries and femoral veins were exposed for cannulation.

Blood pressures from intravascular cannulas were registered using Statham pressure transducers and a

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Photron multichannel direct writing recorder: (1) from either the femoral or carotid artery and (2) from the right ventricle through a No. 9 cardiac catheter, which had been threaded into position from the femoral vein.

Cardiac output was determined by a modification of the radioisotope dye dilution technic of Huff et al. [*19*] and Veall et al. [*20*] utilizing I^{131}-labeled Rose Bengal. Activity was monitored by a 1 inch scintillation crystal through a lead collimator. The photomultiplier tube output was conducted to a Nuclear Chicago rate meter recording on an Esterline-Angus recorder. The procedure was as follows: (1) With the scintillation crystal positioned directly over the exposed heart, background radiation was recorded. (2) An injection of 5 ml. of I^{131} Rose Bengal (1 μc./ml.) was then quickly made into the right ventricle through the recording catheter. (3) The appearance and disappearance of the I^{131} described a graphic curve that represented the dilution and exponential washout of the isotope from the heart. The area (A) under the washout curve exponentially extrapolated to background was determined by planimetric integration. This area is inversely proportional to the blood flow through the ventricular cavities. (4) The isotope was considered to be completely mixed with the total circulating blood when it reached a temporarily stable equilibrium concentration (before an appreciable amount of the Rose Bengal was taken up by the liver). This state was perceived by the scintillation crystal as a relative plateau, reached thirty to fifty seconds after the cardiac output curve was inscribed. The counts per minute during this equilibrium period minus the background count were taken as the equilibrium concentration (C_e). (5) The equation $C.O. = \frac{C_e}{A}$ expresses the cardiac output in blood volume per minute as the ratio of the concentration of radioisotope at equilibrium (assuming complete mixing) to the area under the isotope washout curve which represents the total activity entering and leaving the heart in unit time. The lead collimator limited the field monitored by the crystal to the heart but could only minimize the activity from the posterior chest wall (the inverse square law).

Although it was possible to sample the blood at intervals and to calculate the blood volume and convert the cardiac output from blood volumes per minute into liters per minute, this was seldom done. Cardiac output in "blood volumes" per minute is directly obtained and is a more meaningful unit of flow than liters per minute.

Coronary blood flow was assessed in several ways. A radioisotope method of measuring blood flow in skeletal muscle [*21*] was modified to measure blood flow in the left ventricular myocardium. Through a No. 27 needle an injection of 0.025 to 0.1 ml. of Na^{22} (0.4 to 1 μc./ml.) was made into the left ventricular myocardium midway between apex and base.

(1) A scintillation crystal with a lead collimator was placed directly over the heart and a graphic record of the disappearance of Na^{22} activity from the myocardium was recorded with the previously described equipment; (2) the disappearance curve appeared to be exponential and approximated a straight line when plotted on semi-log paper. The disappearance half-time ($T\frac{1}{2}$) was obtained from the slope of the semi-log plot. So that coronary blood flow would conform graphically to directional changes of blood pressure, cardiac output and cardiac work, it was expressed as $K = \left(\frac{\ln 2}{T\frac{1}{2}}\right)$, which is the removal rate constant and represents the fraction of the Na^{22} removed per minute.

Although this method is an index of the tissue blood flow only in the neighborhood of injection, this value is assumed to be representative of flow through the whole of the left ventricle. It should be emphasized that this method cannot quantitate coronary blood flow but is useful as an index of directional change in coronary perfusion. In the dose volume range of Na^{22} used there was no apparent dose dependence in the washout slope, although at a volume in excess of 1 ml. there was some dose dependence in the slope.

The reliability of the Na^{22} washout procedure was compared in a number of experiments with concomitant measurements of coronary sinus outflow, which was thought to represent a relatively constant fraction of the coronary inflow. This was performed as follows. Through an incision in the right atrial appendage a special plastic cannula with the end flared was passed into the coronary sinus and tied into place. A glass T tube was connected from the coronary sinus cannula to the femoral vein for return of sinus outflow. Coronary sinus flow was diverted at intervals through the side arm of the T tube into a graduate to measure sinus blood flow and to take blood samples for oxygen determinations. It was found that the Na^{22} washout did conform in direction, but not so well in magnitude, with coronary sinus flow.

The Veno-Arterial Shunt (V-A Shunt) [*18*]. A plastic cannula was inserted into the femoral vein and advanced into the lower inferior vena cava. Through this catheter venous blood drained by gravity into a funnel through a plastic screen impregnated with "antifoam" and was collected in a glass reservoir. From the reservoir the blood was pumped by a sigmamotor pump through large-bore polyethylene tubing which had been passed from the femoral artery into the lower abdominal aorta just above the bifurcation. Air in the reservoir and tubing was flushed with saline solution through a "Y" connection and primed with about 150 to 250 ml. of fresh heparinized donor dog blood. Figure 1 is a diagrammatic representation of the shunt. In several experiments in which high shunt outflow was desired, the jugular vein was cannulated and its outflow also added to the venous

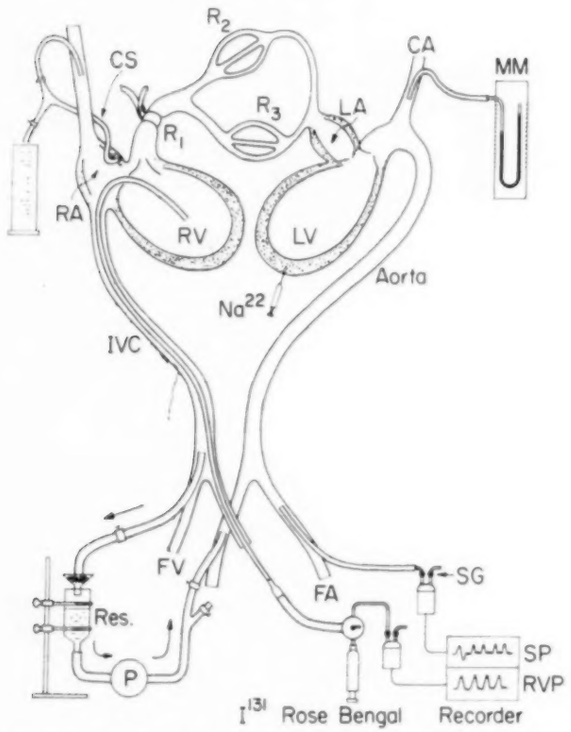

FIG. 1. CS = coronary sinus canula; RA = right atrium; RV = right ventricle; R_1 = resistance of pulmonary artery constricting band; R_2 = resistance of right lung; R_3 = resistance of left lung; LA = left atrium; LV = left ventricle; CA = carotid artery; MM = mercury monameter; Na^{22} = syringe for injecting Na^{22} into myocardium; FA = femoral artery; SG = strain gauge; SP = systemic pressure; RVP = right ventricular pressure; FV = femoral vein; Res. = reservoir; P = pump; IVC = inferior vena cava.

reservoir. When the shunt was not in operation the venous and arterial catheters were clamped.

Calculations. Mean blood pressure was calculated using the formula

$$\overline{BP} = \text{diastolic} + \frac{\text{systolic} - \text{diastolic}}{3}$$

Potential minute work was estimated as blood volumes X mm. Hg/minute by multiplying the cardiac output in blood volumes per minute by the $\overline{BP}$. Stroke work was obtained by dividing minute work by the heart rate.

Experimental Procedures. A plastic adjustable band was placed around the main pulmonary artery trunk for purposes of controlled constriction. Time was allowed for the animal to stabilize after all surgical manipulation and catheter placement had been accomplished, after which resting control measurements of cardiac output pressures and coronary circulation were made. The latter determinations were made either by Na^{22} washout or by measuring coronary sinus flow. Both measurements were carried out simultaneously on five occasions.

When control data had been obtained, the pulmonary artery was gradually constricted by tightening the plastic band until cardiac distress became established as judged by the development of systemic hypotension, cardiac dilatation, cyanosis and impaired contractility (often a drop in heart rate). Serial cardiac output measurements were obtained and coronary blood flow determined. Blood samples from the coronary sinus and a systemic artery were taken in a number of experiments for oxygen determinations.

The amount of constriction necessary to produce cardiac distress varied with each animal. We attempted to achieve various levels of distress ranging from moderately reduced systemic pressure (60 mm. Hg) and cardiac output, to the extreme of cardiac standstill which was carried out in ten of the experiments. An attempt was made to make all physiological measurements during reasonably stable periods, which could be maintained for five or ten minutes or at least for the duration of a particular determination. It took three to six minutes to measure the Na^{22} removal rate adequately. Experiments in which stability of the preparation was questionable were abandoned.

At some stable point of cardiac distress the veno-arterial shunt was started by removing the clamps from the cannulas and starting the pump motor. The shunt flow rate was manually regulated by adjusting the speed of the pump to the rate of venous inflow so as to maintain a steady blood level in the reservoir. The pump flow varied in each experiment and ranged from about 150 to 450 ml. per minute (15 to 20 per cent of the cardiac output). The optimal pumping rate, the point at which pump output was just balanced by venous inflow, quickly became apparent and thereafter the pump seldom required adjustment. Physiological measurements were repeated with the shunt in opertion. The veno-arterial shunt was discontinued at various intervals and repeat measurements made; the shunt was restarted when and if the heart failed again.

RESULTS

Table 1 summarizes the data in forty-one experiments on twenty-three dogs.

Consequence of Pulmonary Artery Constriction (PAC) on Cardiac Performance. Immediately following constriction of the main pulmonary artery, right ventricular pressure increased precipitately and systemic systolic, diastolic and pulse pressures, as well as cardiac output, fell.

When only moderate constriction was applied, the increase in right ventricular pressure often overcame the flow-limiting effect of the constriction and within a two to five minute period cardiac output and systemic blood pressure

TABLE I

CARDIAC WORK IN RELATION TO CORONARY BLOOD FLOW

Mean Values (41 experiments in 23 dogs)	A	Pulmonary Artery Constriction					G
		B	C	D	E	F	
	Control	Heart Failure*	Veno-Arterial Perfusion First Period	Stop Perfusion†	Veno-Arterial Perfusion Second Period	Accommodation‡	Postexperiment Control§
Heart rate (beats/min.)	155 (112–274)	114 (0–210)	120 (46–210)	95 (20–136)	116 (44–164)	124 (80–164)	130 (96–164)
Right ventricular pressure (mm. Hg)	12/1 (8/0–40/0)	20/8 ($\bar{2}$–48/17)	41/17 (12/6–85/40)	12/5 (8/1–20/6)	32/12 (15/5–80/25)	37/11 (20/0–40/20)	12/0 (6/0–20/1)
Mean systemic pressure (mm. Hg)	99 (59–137)	20 (11–63)	77 (32–113)	40 (29–67)	82 (39–119)	98 (82–130)	83 (45–105)
Cardiac output (blood vol./min.)	1.7 (0.9–2.5)	0.2 (0–0.6)	0.8 (0.4–1.8)	0.3 (0–1.0)	0.8 (0.5–1.4)	0.9 (0.5–1.7)	1.5 (0.9–1.8)
Left ventricular work (blood vol. × mm. Hg/min.)‖	169 (72–286)	8 (0–38)	64 (19–145)	15 (0–67)	73 (20–149)	84 (41–117)	122 (63–185)
Left ventricular stroke work (blood vol. × mm. Hg/stroke)¶	1.1 (0.4–2.1)	0.1 (0–0.2)	0.6 (0.2–1.3)	0.2 (0–0.5)	0.6 (0.3–1.2)	0.7 (0.3–1.3)	1.1 (0.4–1.3)
Relative coronary blood flow as Na^{22} removal rate constant (per cent/min.)**	35 (32–40)	5†† (greatly prolonged)‡‡	45 (23–82)			35.7 (34–36)	

* Ventricular standstill in ten experiments.
† Ventricular standstill in five experiments.
‡ Eight animals accommodated.
§ Fourteen experiments.
‖ Cardiac work (blood vol. mm. Hg/min. = cardiac output × systolic $\bar{B}\bar{P}$).
¶ Stroke work (blood vol. mm. Hg/stroke = cardiac output × $\bar{B}\bar{P}$/rate).
** Determined in eight experiments ($\ln 2/T\frac{1}{2} \times 100$).
†† $T\frac{1}{2}$ during ventricular standstill was infinitely prolonged in two dogs (no coronary blood flow).
‡‡ Two determinations.

would increase and stabilize at levels approaching control values. In these instances coronary blood flow (CBF) was noted to increase, confirming the earlier observations of Gregg and Shipley [*22*] that CBF increased with increased ventricular work and in contradiction to the findings of Anrep and Hausler [*23*] and Davis [*24*] on this point.

The "intrinsic compensation" (associated with an increase in CBF) soon failed as the PAC was further increased, for then the continued fall in systemic blood pressure and cardiac output led to a *fall* in CBF. This was followed by a gradual decline in the vigor and amplitude of contractions, together with progressive cardiac cyanosis and dilatation. The marked rise in right ventricular pressure to two or three times the control level was only transiently sustained, falling as the heart failed, but generally settling at systolic and diastolic levels somewhat above control values. (Table I, column B.)

A typical response to PAC is shown in Figure 2A by the records obtained during one such experiment. In this experiment PAC was designed to provoke near ventricular standstill. To achieve ventricular standstill, PAC had to be carried to about 80 per cent obstruction of the lumen and adjusted several times. (Fig. 2A, PAC increased.) The deterioration of cardiac working ability is clearly indicated by the decline in pressures, heart rate and cardiac output. Concomitantly there was a marked decrease in coronary blood flow as indicated by prolongation of the Na^{22} disappearance $T\frac{1}{2}$ to twenty-two minutes from a control $T\frac{1}{2}$ of two minutes. (Figs. 2A and 2B, slope A.)

Furthermore, it was demonstrated in a number of animals that once heart failure became well established, even release of PAC did not significantly improve cardiac functional capacity or cause a decrease in size.

Effect of the Veno-Arterial Shunt on Heart Failure

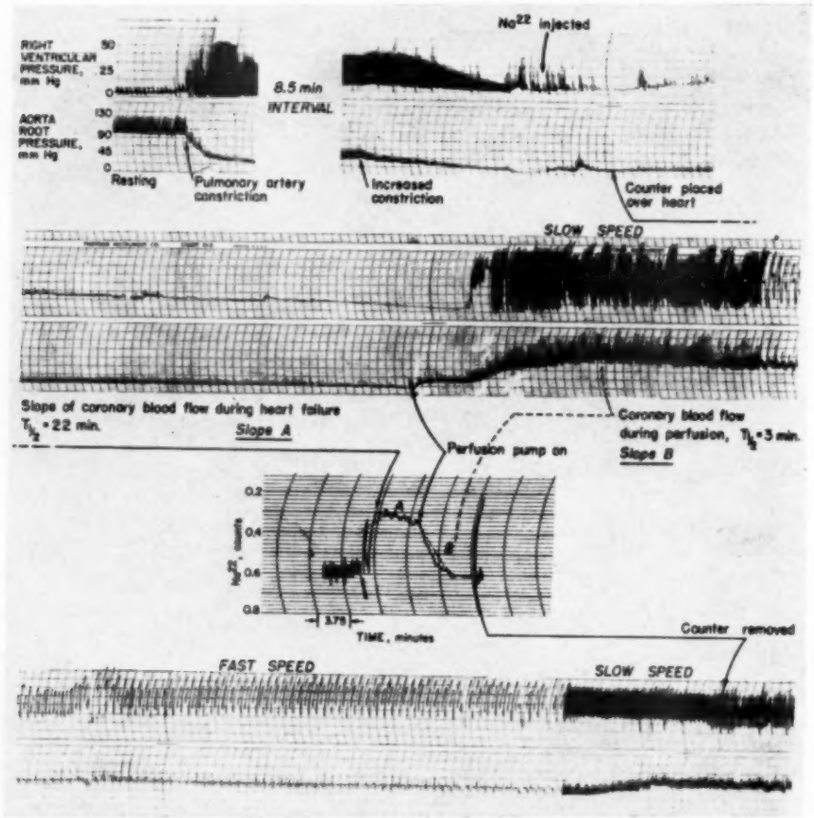

FIG. 2A. Experiment 15. Dog 20.4 kg. Pressure curves and Na^{22} washout curve (third strip) taken simultaneously. After heart failure was established, an injection of 0.1 ml. Na^{22} was made into the myocardium and the counter placed over heart (top strip). Arrows indicate coincident time on pressure strips and rate meter record starting at the beginning of slope A. With the heart in failure Na^{22} washout is prolonged, because of poor coronary circulation, to a disappearance $T\frac{1}{2}$ of twenty-two minutes (slope A) from control $T\frac{1}{2}$ of two minutes (not shown). Turning the perfusion pump on (second strip) abruptly steepens the washout slope as CBF increases (slope B). This is quickly followed by a progressive increase in right ventricular pressure, aortic root pressure and stroke output as cardiac function is revived by the V-A shunt (second and last strips). The apparent lag in right ventricular recovery behind recovery of aortic root pressure is artifact caused by I^{131} dye injection for cardiac output determination. Recovery was sustained for several hours while V-A perfusion was maintained.

and Shock [*18,25,26*]. After heart failure had advanced to the stage where, in our experience, release of the PAC alone would probably not have appreciably restored ventricular working capacity, V-A shunting was started, with the fixed PAC maintained. Starting the pump elevated arterial pressure mechanically and within a few seconds there was a return and progressive increase in the vigor and amplitude of successive contractions of both ventricles, with proportionally increased stroke output. (Figs. 2A and 3; Table 1, column C.) These strengthened ventricular contractions rapidly increased systemic pressure well beyond the capacity of the pump alone, clearly showing that arterial pressure was being predominantly determined by the contracting heart itself.

Associated with this improvement was a sharp fall in jugular venous pressure (an index of right ventricular filling pressure) to about 9 to 10 cm. H_2O) from the extreme elevations (20 to 30 cm. H_2O) recorded prior to V-A shunting.

Even with the heart almost at ventricular standstill (Fig. 2A) only a few seconds were required for the pump to raise arterial pressure to 40 mm. Hg, after which ventricular contractions reappeared. Right ventricular pressure increased to three or four times control values,

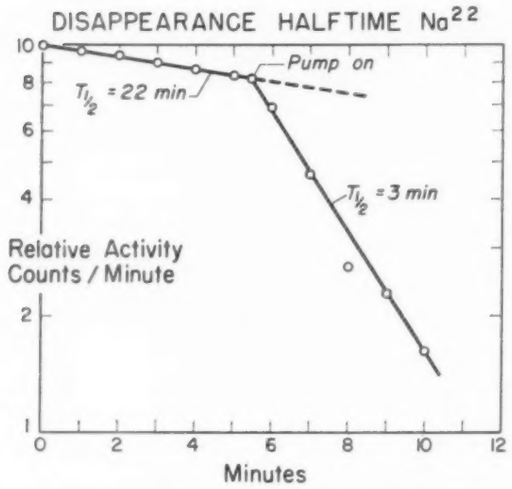

FIG. 2B. Experiment 15. Semi-log plot of Na^{22} washout curve shown in Figure 2A.

markedly exceeding even the high values observed immediately following pulmonary artery constriction; at the same time systemic pressure had increased almost to control levels. The tiny pump undulations were clearly distinguishable from the ventricular contractions as they reappeared. (Fig. 2A, perfusion pump on.)

Contractions returned or improved simultaneously in both ventricles, although rarely left ventricular contractions appeared to precede contractions of the right ventricle by a beat or two. The resulting improvement in cardiac performance could be maintained for many hours or for as long as V-A perfusion was continued.

Probably the most striking response to veno-arterial perfusion was the visible progressive decrease in the size of the heart and the rapid disappearance of cyanosis while the pulmonary artery remained constricted. These changes started during the first few seconds, and were invariably associated with sharply increased coronary blood flow as well as visible improvement of myocardial contractility.

In a few of the animals in which the pulmonary artery had been markedly constricted, cardiac performance improved transiently (two to ten minutes) but ventricular function then gradually deteriorated despite continuation of the V-A shunt. This occurred only in those animals in which PAC had almost totally occluded the lumen of the vessel, in which case ventricular contractions, however, vigorous, could not eject enough blood past the constriction to sustain cardiac function. In such instances release of the pulmonary constriction alone did not revive the heart; but if V-A shunting was started in addition, recovery quickly followed.

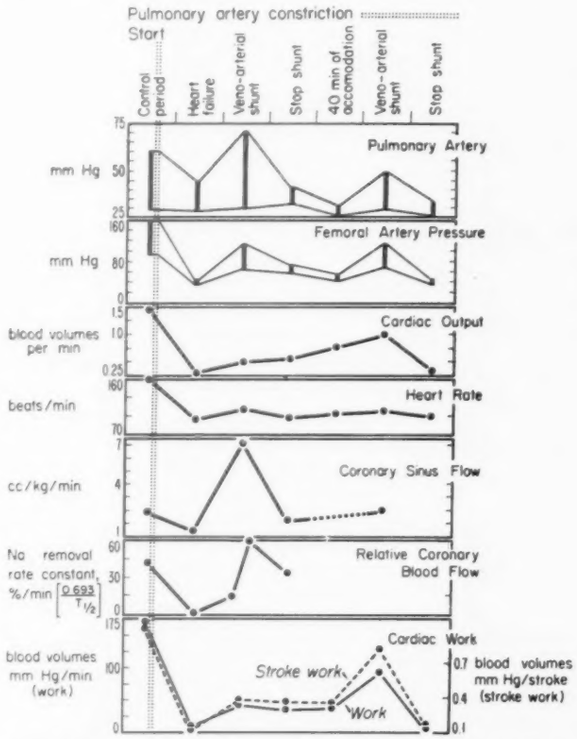

FIG. 3. Experiment 18. Dog 18 kg. After PAC is applied, cardiac working capacity and CBF drop sharply. During V-A shunting CBF soars and working capacity is markedly improved, overcoming the unaltered PAC. V-A shunting was continued for forty-five minutes without change in performance level. When the shunt is discontinued there is a gradual decline in working capacity over a forty minute period in contrast to the abrupt incapacitation initially provoked by PAC. CBF during this period exceeds the first failure period. Cardiac output continues to increase as the pulmonary artery pressure distal (not shown) to the PAC falls.* The second period of V-A perfusion restores cardiac working capacity even more effectively but is not sustained when the shunt is stopped.

* Right ventricular pressure or pulmonary artery pressure measured proximal to the PAC band is determined not only by the resistance imposed by the constricting band but also by the combined resistance of the pulmonary vessels distal to the constriction. $R_T = R_1 + R_2, R_3$ (Fig. 1). PAC sometimes provokes marked reflex spasm of the distal pulmonary vessels resulting in increased pulmonary vascular resistance, which may fall during or following V-A shunting.

"Accommodation" Phenomenon. With the V-A shunt in operation, the capacity of the heart to perform work in the majority of animals strikingly increased, within two to six minutes reaching a stable level that could be maintained for hours. (Table I, column C.) If the V-A shunt

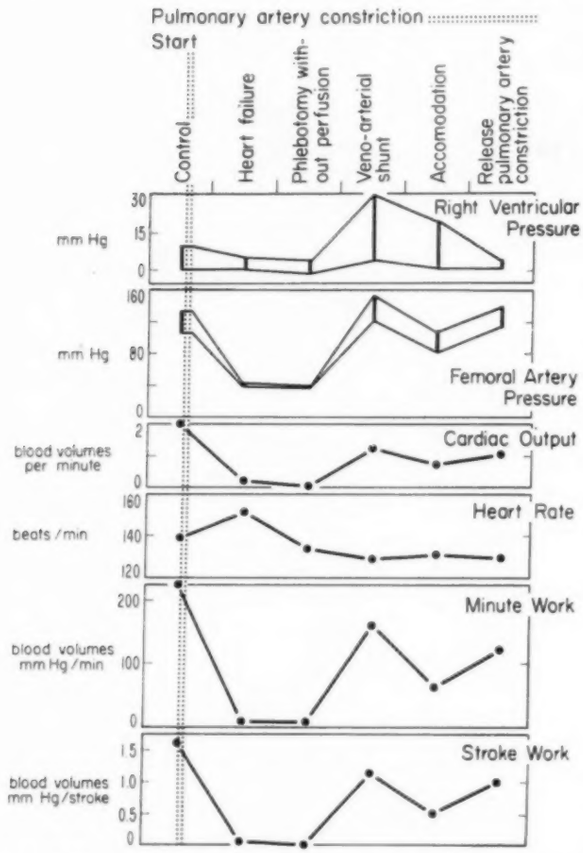

FIG. 4. Experiment 8. Dog 16.2 kg. Study of venous limb of shunt. After heart failure is established, phlebotomy causes further rapid functional deterioration. Prompt recovery follows when the arterial limb of the V-A shunt is added and is sustained for an arbitrary period of twenty-five minutes. In this animal "accommodation" persisted at a high performance level for forty-eight minutes with only a modest improvement on release of the PAC (see text).

was then discontinued after a stable level of performance was achieved and maintained, there was usually a sharp decline in all parameters of cardiac performance, either rapidly or over a one to ten minute period (Table I, column D); such deterioration of cardiac working ability could be rapidly reversed by resuming operation of the V-A shunt. (Table I, column E and Figs. 2A and 3.)

During the course of an experiment the shunt was halted at variable intervals to assess the level of cardiac performance. During early experiments with this procedure it was noted that in some instances the heart continued to perform well for long periods after V-A perfusion had been discontinued despite the presence of the PAC. This acquired capacity of the heart to adjust to and sustain a work load under conditions that had previously severely impaired its performance or had caused complete cardiac standstill was termed "accommodation." (Table I, column F and Fig. 3.)

The accommodated state was allowed to persist and was observed over periods of from ten to fifty minutes in order to study the characteristics and duration of this compensatory phenomenon. Accommodation was achieved in eight experiments after six to twenty-eight minutes of V-A perfusion. Several animals accommodated several times to serial increases in the degree of PAC, and in a few instances repeated accommodation to serial increases in PAC was observed even in animals that had been previously asystolic.

The ability of an animal to accommodate seemed to depend primarily upon the duration of V-A perfusion, the severity of constriction, and to some extent upon individual variation. A sustained increase in coronary blood flow above control levels was consistently noted in animals that accommodated. (Table I, column F.)

Evaluation of the Effect of the Veno-Arterial Shunt on Cardiac Performance. In order to clarify the basis by which the V-A shunt procedure implemented cardiac work capacity, the components were separately studied: (1) the effect of phlebotomy alone without arterial perfusion and (2) arterial perfusion without phlebotomy (in effect, arterial transfusion with the pump).

It could be argued that if the venous drainage from the inferior vena cava into the reservoir lowered the blood volume of the right side of the heart, this might conceivably reduce the diastolic size of the dilated heart and presumably promote return from the descending limb of Starling's curve to the ascending side of the curve [9].

Figure 4 shows a representative experiment to test this premise. After heart failure was established, the vena cava catheter was opened and blood was allowed to drain freely into the reservoir without being pumped to the arterial side of the circulation. Phlebotomy without arterial perfusion invariably resulted in rapid deterioration in cardiac function, usually to cardiac standstill after even small amounts of blood were allowed to drain, thus precluding the "Starling effect" as a factor in the recovery of function. When the arterial limb of the shunt was added, however, cardiac function quickly improved.

Figure 5 illustrates the reverse of this experiment: blood was pumped into the arterial side of the shunt from the reservoir without concomi-

tantly withdrawing blood from the venous side of the system. The level of the reservoir was maintained by adding donor blood or normal saline solution. Rapid arterial transfusion was clearly effective in improving cardiac function during the early minutes of pumping. Within a short time, however, when the increase in circulating volume became too great, function declined unless the venous side of the system was also opened and the increment in volume gradually removed from the circuit. When this was done the usual stable improvement in cardiac working ability was noted. (Fig. 5.) This observation may explain the transient benefits following arterial transfusion for shock following myocardial infarction [*27*]; an increment in arterial pressure improves coronary perfusion but the excessive increase in blood volume proves ultimately deleterious to the already severely stressed heart.

The effect of arterial transfusion was further studied by injecting blood into the femoral artery with a pressure bottle. Cardiac performance improved during the course of administration of two 400 cc. bottles of donor blood, but then gradually returned to failure levels after a brief period of operation with the increased blood volume.

In the failing heart, slow V-A shunting did not improve heart function unless the flow rate was rapid enough to elevate systemic blood pressure to between 30 to 40 mm. Hg, at which level ventricular contractions usually became stronger. In contradistinction to this, intravenous infusion of blood, particularly when rapid, invariably depressed cardiac function. It thus seemed clear that changes in blood volume do not account for the efficacy of the V-A shunt procedure.

Blood oxygen contents determined during the experiment shown in Figure 3 clarify several important effects of V-A shunting. Arterial samples from the aortic arch and venous blood from the coronary sinus were: 21.10 and 4.86 vol. per cent, respectively, during the control period; 22.13 and 2.88 vol. per cent during heart failure; 18.85 and 8.00 vol. per cent during V-A shunting; 21.4 and 5.54 vol. per cent during accommodation.

It was apparent that venous blood shunted intra-arterially was not entering the upper aorta; indeed, samples taken as low as the renal arteries were fairly well oxygenated (80 per cent). The shunted venous blood was found to have gone predominantly into the opposite femoral artery and lower abdominal aorta. The

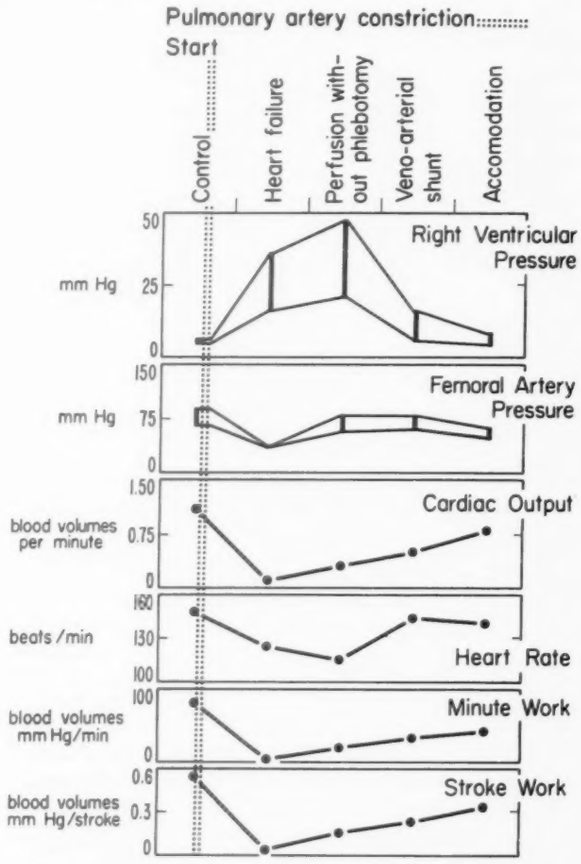

FIG. 5. Experiment 11. Dog 18.1 kg. Study of arterial limb of shunt. After heart failure is established, working capacity increases sharply, concomitantly with rapid arterial infusion of blood from the reservoir. Cardiac work capacity increases further when the venous limb is added. When shunt was discontinued accommodation persisted at a high level. The fall in right ventricular pressure started several minutes after V-A perfusion began and probably represents a decrease in pulmonary vascular resistance distal to the PAC.

hydraulic effect of the unoxygenated shunted blood was thus apparently forcing well oxygenated blood (from the left ventricle) through the coronary and cerebral circulations.

Coronary Blood Flow and Cardiac Performance. Once it was established that raising arterial blood pressure was the critical factor which brought about a functional recovery of the myocardium, the most obvious pressure dependent factor to consider was the coronary blood flow.

A decrease in CBF was regularly observed coincident with the decline in cardiac output and systemic blood pressure that followed PAC; whereas V-A perfusion associated with recovery of cardiac function invariably caused an increase of CBF. The increase in CBF was repeatedly

noted to precede the improvement of cardiac output as well as the ventricular component of systemic blood pressure. (Figs. 2A and 3.)

When an injection of Na^{22} was made into the failing left ventricle the disappearance of the isotope was slow and prolonged ($T\frac{1}{2}$, twenty-two minutes), giving a shallow washout slope (Fig. 2A, slope A, Fig. 2B) representing poor coronary blood flow. When the V-A shunt was started (Figs. 2A and 2B, perfusion pump on) there was a sharp increase in the rate of Na^{22} disappearance and the washout slope became steep (slope B), indicating an increase in CBF. Coincident with the increased CBF was the marked increase in ventricular working ability indicated by the sharp climb in systemic and right ventricular pressures as well as tripling of the cardiac output.

In the same experiment the progressive increase in cardiac output that accompanied V-A perfusion could be appreciated in its earliest phase when an injection of I^{131}-labeled Rose Bengal (to measure cardiac output) was made into the right ventricular cavity during severe heart failure. The washout slope of the dye was shallow and prolonged—flat when the animal became asystolic. After the V-A shunt was started nothing happened for several seconds until ventricular contractions returned, then the washout slope began to steepen rapidly as the resumption of contractions expelled the isotope from the heart.

Figure 3 illustrates a similar relationship between coronary blood flow and ventricular performance in a less drastically impaired heart. When the CBF was low, there was an associated impairment in the ability of the ventricle to perform external work. When the CBF was increased by V-A perfusion, ventricular working ability was concomitantly enhanced. In this experiment Na^{22} removal and coronary sinus outflow were compared and it was verified that in direction and relative magnitude Na^{22} removal rate was a valid index of CBF.

COMMENTS

When a portion of the myocardium is acutely deprived of its blood supply by experimental coronary occlusion it ceases to contract in three to four seconds [*12*], and within a minute this potentially infarcted area stretches rather than shortens with each heartbeat [*13*]. Case, Berglund and Sarnoff [*14*] have demonstrated a stepwise decline in the ventricular function curves obtained by plotting stroke work against increasing atrial pressure when the coronary blood flow is limited by coronary artery constriction. Gregg [*15*] has noted that following experimental coronary artery occlusion there is an immediate impairment of cardiac function, associated with decreased pressure amplitudes, reduced stroke output and cardiac dilatation.

Cardiac function is severely impaired when the main pulmonary artery is sufficiently constricted so that the left ventricle is inadequately filled and hence cannot maintain systemic pressure or cardiac output sufficient for coronary perfusion. Although the sharp increase in CBF immediately following PAC [*15b*] probably enables the myocardium, at least initially, to compensate for the increased load, CBF soon falls and the heart fails rapidly. The suggestion that reduced CBF was a factor in the ultimate failure of the right ventricle following PAC was advanced many years ago by Feinberg and Wiggers [*28*] although they lacked CBF measurements to confirm this. Because our measurements indicate that the heart does not fail after PAC *until* CBF falls, it seems quite probable that the loss of working capacity is a consequence of insufficiency of the coronary circulation to support myocardial metabolism, a mechanism analogous to the cardiac collapse that results from direct coronary artery ligation.

PAC has been shown to produce chronic heart failure characterized by sodium retention, ascites and edema, which responds to digitalis therapy with diuresis and general improvement in cardiac function [*29*]. Failure of spontaneous functional recovery to occur upon removal of the constriction [*31*] suggests that sustained heart failure caused by PAC is fundamentally metabolic.

The improvement of coronary circulation effected by V-A perfusion appears to trigger the myocardium into contracting more forcefully. The increment in contractile capacity so acquired enables the right ventricular myocardium to increase intraventricular pressure enough to overcome the fixed mechanical obstruction imposed by the constriction. The strengthened left ventricular contraction increases stroke volume in the face of an increased load (the systemic pressure elevation caused by the V-A shunt), thus increasing the total stroke output of both ventricles. In a short time the cycle of increased blood pressure (produced by the pump) → increased coronary blood flow →

increased vigor of contraction → increased stroke output by ejection of a greater fraction of the residual volume (heart gets smaller) → further increase in arterial pressure (by the recovering heart) → further increase in coronary blood flow progresses to a markedly improved level of cardiac performance despite persistence of the previously disabling PAC.

The dilated, poorly contracting heart, distended with blood, literally shrinks; its contractile vigor returns, and cyanosis disappears as coronary blood flow increases during V-A perfusion. Both the improvement in color and the threefold increase in coronary sinus oxygen content clearly reflect the increased availability of oxygen to the myocardium and directly demonstrates that CBF and myocardial metabolism are critical determinants of heart size. Furthermore, it is clear that heart size can be altered independently of the load. Thus heart size decreases while the disabling obstruction to right ventricular outflow remains unchanged; the load on the left ventricle increases as the systemic pressure rises.

In addition to determining the availability of oxygen and metabolic substrate, the coronary circulation carries away metabolic products in its venous outflow. Studies on coronary sinus blood from our failing dog hearts indicate that substances capable of depressing myocardial contractility and diastolic tone often accumulate when coronary circulation is very deficient. Under other experimental conditions the coronary sinus blood from our animals often contained substances that augment contractility and tone [*32*].

Sayen et al. [*33*], using a polarographic technic, have noted that regional myocardial contractility is to some extent independent of tissue oxygenation. We have observed that when the heart is functionally depressed by poor coronary circulation the recovery of contractile strength that accompanies improvement in CBF is more critically related to factors other than increased delivery of oxygen to the myocardium. This was demonstrated in an experiment designed to study the efficacy of the V-A shunt delivering the blood to the carotid artery as compared to the femoral artery under identical conditions in the same animal.

A Hufnagel valve was implanted in the thoracic aorta to prevent the venous blood shunted to the femoral artery from entering the aortic arch (although this was minimal even without the valve). It was found that good functional recovery followed V-A perfusion through either vessel, although the oxygen saturation of aortic arch samples was 11.20 vol. per cent during carotid perfusion as compared with 20.08 vol. per cent during femoral artery perfusion.

Although it has been shown that hypoxia disturbs lactate, pyruvate and glucose extraction, and raises the threshold for lactate and pyruvate utilization by the heart [*34*], hypoxia clearly is only part of the story. There may be simultaneously an accumulation of metabolites, particularly products resulting from myocardial hypoxia, such as lactic acid, that are capable of deleteriously affecting ventricular function, and their washout may be an important factor in the functional recovery associated with improvement in coronary circulation [*32*].

In making such diverse adjustments as those required during exercise [*4,5*], under the influence of sympathetic stimulation [*15c,35*], catecholamines [*36*], digitalis [*37*], and in the presently demonstrated entry and emergence from heart failure, the performance of the heart frequently does not conform to the Frank-Starling relationship. Sarnoff [*2*] has attempted to reconcile the observed inconsistencies by developing the concept of a "family of Starling curves" and has demonstrated that the performance of the heart may conform to Starling's law under a variety of experimental conditions, each of which may give rise to a new curve. He implies that the response of the heart may change from one curve to another when "some influence of physiologic importance occurs" [*2*]. It seems probable that each new curve represents some change in the metabolic state of the myocardium. While this is evidence that this basic property of muscle probably holds for a variety of metabolic states it does not clarify the extent, if any, to which the intact animal utilizes this mechanism for regulation. Since it is unlikely that important changes in cardiac performance occur without an intimately associated change in myocardial metabolism, it is reasonable to consider how this factor may operate as a direct determinant of performance without recourse to the Starling mechanism.

Increases and decreases in cardiac work are usually accompanied by relatively proportional increases and decreases in coronary blood flow, whereas cardiac size often tends to vary inversely with CBF. The heart gets smaller during

exercise [*5*] at a time when CBF is undoubtedly increasing. Pitressin, which sharply decreases CBF, concomitantly causes cardiac dilatation [*17*] and lowers cardiac output without lowering systemic blood pressure [*16*]. Increased CBF is observed in the exercising closed-chest dog [*38*] and during the passive increase of ventricular work induced by pulmonary artery or aortic constriction [*15b*]. Gregg observes that when stimulation of cardiac sympathetic nerves causes an increase in CBF, there is invariably gross visual evidence of increasing vigor of cardiac contractions or measurably increased cardiac work and/or metabolism [*15c*]. This increase in CBF is regarded by Gregg as "a secondary phenomenon resulting from coronary dilatation occasioned by chemico-metabolic influences incident to the increased work and metabolism" [*15c*].

As our failing dog hearts respond to V-A perfusion, an increase in CBF is invariably noted to *precede* the recovery of contractile vigor and myocardial tone (decrease in heart size). This increase of CBF, through an effect on myocardial metabolism, is regarded as the primary stimulus for improvement of ventricular performance and decrease in heart size. Although we cannot exclude some unknown humoral or reflex effect associated with increased systemic pressure, such effects, if they occur, would probably be minimized by anesthesia. Recovery, moreover, has never been noted in the absence of an increment in CBF.

The close parallelism between cardiac work and CBF underscores the dependence of the heart upon increased metabolism (through increased CBF) to support an increase in effort. The next question is whether a primary increase in CBF can drive the heart to work harder by forcing a change in cardiac metabolism. It has been shown in the dog that cardiac oxygen consumption at rest increases when oxygen availability is increased by increasing CBF [*39*]. We have also observed this finding and in addition note that when a forced increase in CBF is imposed it usually drives the resting anesthetized dog heart to work excessively in the absence of any other apparent stimulation to alter its performance [*40*].

The present observations, that cardiac size and cardiac contractile strength may be determined by the level of coronary circulation, intimately link the coronary blood flow with cardiac performance. Such a link suggests that the strength of a given contraction (or sequence of contractions) and myocardial tone (which influences diastolic volume) are ultimately determined by metabolic factors. These factors are in turn influenced by the dynamic interaction of (1) the coronary inflow bringing oxygen, metabolic substrate and humoral substances to the myocardium, (2) by coronary outflow washing out CO_2 pressor and suppressor metabolites, (3) the interplay, release and washout of autonomic nervous system mediators (such as nor-epinephrine) in the myocardium [*41*]. The incorporation of myocardial metabolism (as influenced and limited by coronary circulation) into the dynamic process of regulation of cardiac performance reconciles many well established observations and, indeed, some of Starling's own data [*42*].

There are important clinical ramifications that follow from considering that when shock and heart failure result from deficient coronary circulation, they can be reversed by improving coronary circulation. It seems clear that when systemic blood pressure falls significantly during shock (from any cause), at some point CBF decreases despite maximum coronary dilation brought about by hypoxia. Failure of the coronary circulation provokes a critical decline in cardiac working capacity which then becomes an ultimate factor in sustaining the hypotension and shock. From results obtained in the dog, it might be anticipated that persistent shock and some forms of heart failure seen clinically might be reversible by use of the V-A shunt procedure.

It is well known that one of the important factors sustaining hypotensive shock following myocardial infarction is a fall in blood flow to the viable myocardium. We have used the V-A shunt in a seventy-six year old patient who appeared to be moribund after ten hours of shock and four hours of pulmonary edema following her second myocardial infarction [*43*]. After seventy minutes of V-A shunting, pulmonary edema cleared and she became normotensive. The patient remained normotensive and free of heart failure for the next five days, after which she died of non-related causes. This case will be reported in detail in another communication.

SUMMARY

The manner and extent to which the coronary circulation affects myocardial contractility and cardiac size were explored.

It was found that heart failure induced by

pulmonary artery constriction is essentially metabolic, a consequence of decreased coronary blood flow.

Whereas release of pulmonary artery constriction did not restore cardiac working capacity once failure was established, marked functional improvement could be consistently obtained by increasing coronary blood flow by means of a simple veno-arterial shunting procedure, in the face of persistent pulmonary artery constriction. This was to some extent independent of the oxygen tension of the coronary arterial blood.

After a period of veno-arterial shunting, some of the animals acquired the capacity to maintain good cardiac function even when the shunt was discontinued, despite continuance of the previously disabling pulmonary artery constriction. Such an adjustment depended upon a sustaining elevation of CBF after the shunt was discontinued. This *accommodation phenomenon* demonstrates the remarkable capacity of the heart to recover when given temporary assistance that improves the metabolic milieu.

The coronary blood flow has been shown to influence the heart size, the strength of contraction, and adaptive mechanisms to increased work loads. A simple "Starling relationship" therefore cannot explain the control of the *in vivo* cardiac performance observed in these experiments.

The clinical ramifications of these observations on the interpretation and management of shock and some forms of heart failure are discussed. Clinical application of the principles is described in a patient with myocardial infarction and prolonged shock.

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Calcification of the Pulmonary Artery in Patent Ductus Arteriosus with Reversal of Blood Flow*

Report of Four Cases

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ISOLATED patent ductus arteriosus with a characteristic left-to-right shunt is usually easily diagnosed by recognition of the typical continuous cardiac murmur [*1–3*]. On the other hand, the diagnosis of patent ductus complicated by pulmonary hypertension and reversal of blood flow may be very difficult [*3–5*]; the symptoms and signs produced by the resultant bidirectional or right-to-left shunt are often mistaken for those of other congenital or acquired lesions [*6,7*]. Recent observations of characteristic calcification of the pulmonary artery in four adult patients indicate that this finding may not be as rare as it is reputed to be, and that when present this roentgenographic sign is a valuable clue for diagnosis of patent ductus arteriosus with reversal of flow.

The literature contains isolated reports of pulmonary arterial calcification in patients with patent ductus arteriosus with reversed shunt [*3,6,8–10*]. However, no paper deals with the diagnostic significance of this important sign. It is the purpose of this communication to report the clinical findings in four patients with patent ductus with reversed shunt, all of whom showed calcification of the pulmonary artery on roentgenographic examination.

CASE REPORTS

CASE 1. A forty-seven year old woman (No. 2363) was admitted to St. Francis Hospital and Sanatorium on September 5, 1956, complaining of dyspnea, cyanosis and polycythemia. She had had a cardiac murmur since childhood. In 1940 it was discovered that she had polycythemia. In 1943 the first episode of recurrent hemoptysis occurred. At that time, there was easy fatiguability and dyspnea on slight to moderate exertion. In April 1950, she had acute chest pain. In March 1956, increasing exertional dyspnea and polycythemia were noted. Radioactive phosphorus was administered with temporary reduction of the erythrocyte count. In June 1956 she was admitted to another hospital because of heart failure and fever. Subacute bacterial endocarditis was suspected, but blood cultures were sterile. After three weeks of treatment with penicillin her condition improved.

Physical examination on admission to St. Francis Hospital revealed respiratory distress, deep cyanosis of the lips and nail beds, and clubbing of the fingers and toes. The blood pressure was 110/80 mm. Hg. The lungs were clear. Examination of the heart revealed a split second sound at the base. There was a systolic murmur best heard over the left sternal border, and a high-pitched diastolic murmur heard over the pulmonic area. Moderate sacral edema was present and the liver edge was palpable 4 cm. below the right costal margin.

Laboratory data were as follows: hemoglobin, 16.8 gm./100 cc.; erythrocytes 7 million/cu. mm.; hematocrit 53 per cent; leukocytes 6,800/cu. mm. with a normal differential count. Roentgenograms of the chest showed enlargement of the heart and pulmonary artery with striking calcification of the pulmonary artery. (Figs. 1A and 1B.) The electrocardiogram disclosed "incomplete right bundle branch block," right axis deviation, and right ventricular preponderance. (Fig. 1C.) During cardiac catheterization the catheter passed from the pulmonary artery into the aorta via a patent ductus arteriosus. The pulmonary artery pressure was 104/54 mm. Hg; the right ventricular pressure was 125/82 mm. Hg; and

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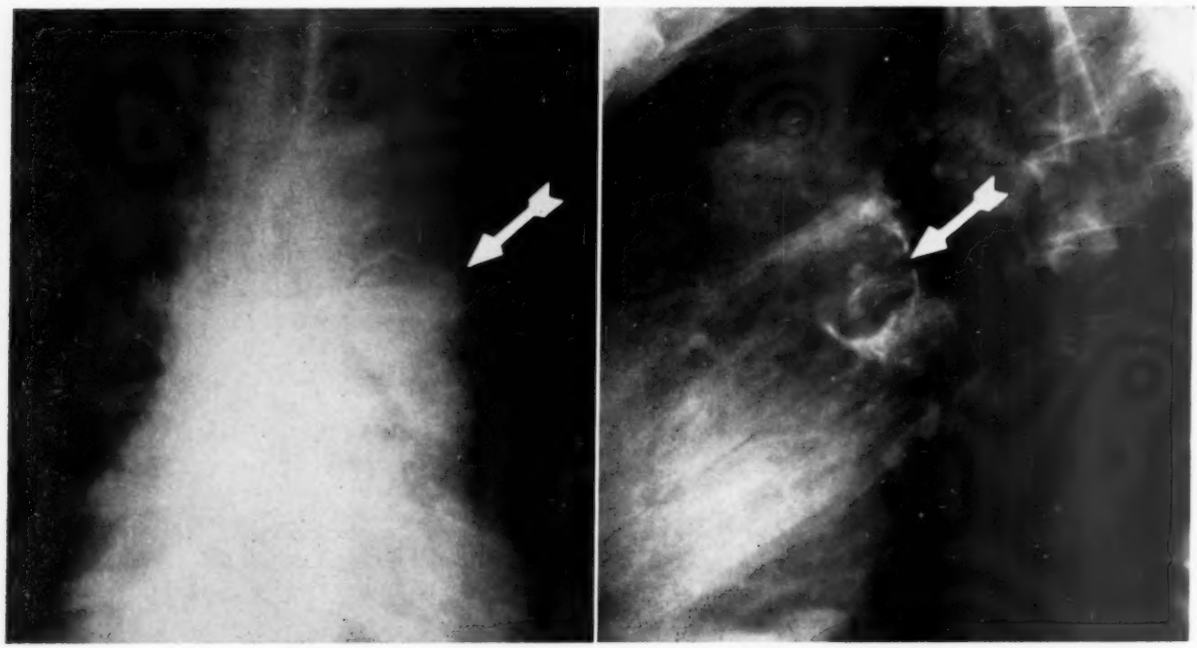


1A 1B

FIG. 1A. Case 1. Conventional frontal teleroentgenogram showing enlargement of the heart and pulmonary artery segment. The left branch of the pulmonary artery (arrow) is calcified. There is also calcification between the pulmonary artery and aortic knob (site of the ductus arteriosus) and the aortic knob.

FIG. 1B. Lateral teleroentgenogram shows the left pulmonary artery almost completely calcified (arrow).

the aortic pressure 112/78 mm. Hg. The blood oxygen content (in volumes per cent) were: pulmonary artery 10.6; right ventricle 9.9; right atrium 9.9; superior vena cava 12.8; and aorta 19.7. The arterial oxygen saturation in the aorta was 90.9 per cent. Angiocardiography demonstrated opacification of the aortic knob and descending aorta simultaneously with the pulmonary artery and its branches. (Figs. 1D, 1E and 1G.) When the left heart was opacified there was filling of the ascending aorta. (Figs. 1F and 1H.) On bed rest, with the administration of digitalis, diuretics and a low sodium diet, the patient improved and was discharged on October 7, 1956.

When last examined on September 21, 1959, the patient had mild cyanosis of the face and upper extremities but pronounced cyanosis of the legs. The lungs were clear, and the heart findings were unchanged. The liver edge was firm, moderately tender, and extended 5 cm. below the right costal margin. The spleen was also enlarged and tender and was palpated 3 cm. below the left costal margin. The hemoglobin was 21.2 gm./100 cc.; erythrocytes 10.4 million/cu. mm. and the hematocrit 68.5 per cent. The roentgenogram of the heart and the electrocardiogram were unchanged.

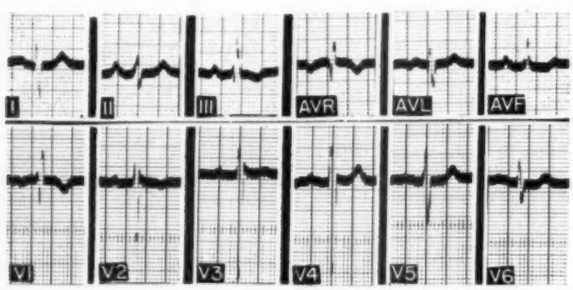


FIG. 1C. Electrocardiogram showing right axis deviation, right ventricular hypertrophy, and the RSR′-V_1 pattern of right ventricular overloading.

CASE II. A sixty-five year old white woman (New York Hospital No. 648405) was admitted on December 19, 1959 because of severe dyspnea and cyanosis. She had been weak and sickly during her childhood, and a diagnosis of congenital heart disease had been made. Since 1949 she had exertional dyspnea, fatigue, occasional episodes of hemoptysis, and slight edema of the ankles. She was first admitted to The New York Hospital on December 6, 1954, because of fever and malaise of two weeks' duration. At that time cyanosis and clubbing of the fingers and toes were noted. The lungs were clear and the heart was moderately enlarged. There was a rough systolic and a loud, blowing early diastolic murmur over the second left intercostal space at the sternal border. The blood pressure was 130/70 mm. Hg.

Laboratory data revealed the following: hemoglobin 18.6 gm./100 cc.; erythrocytes 6.4 million/cu. mm.; and hematocrit 46 per cent. The roentgeno-

FIG. 1D. Frontal angiocardiogram showing a huge right ventricle and pulmonary artery. The aortic knob and descending aorta are opacified via a patent ductus arteriosus demonstrating a right-to-left shunt. The abrupt decrease in size of the right pulmonary artery suggests partial thrombosis of this vessel.

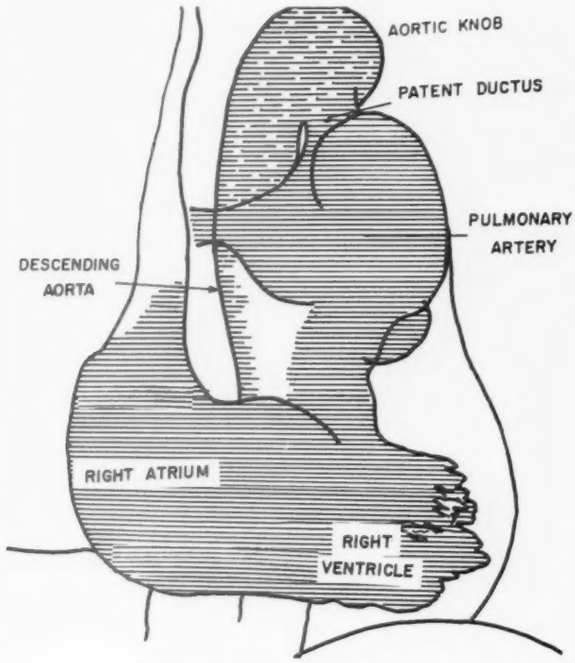


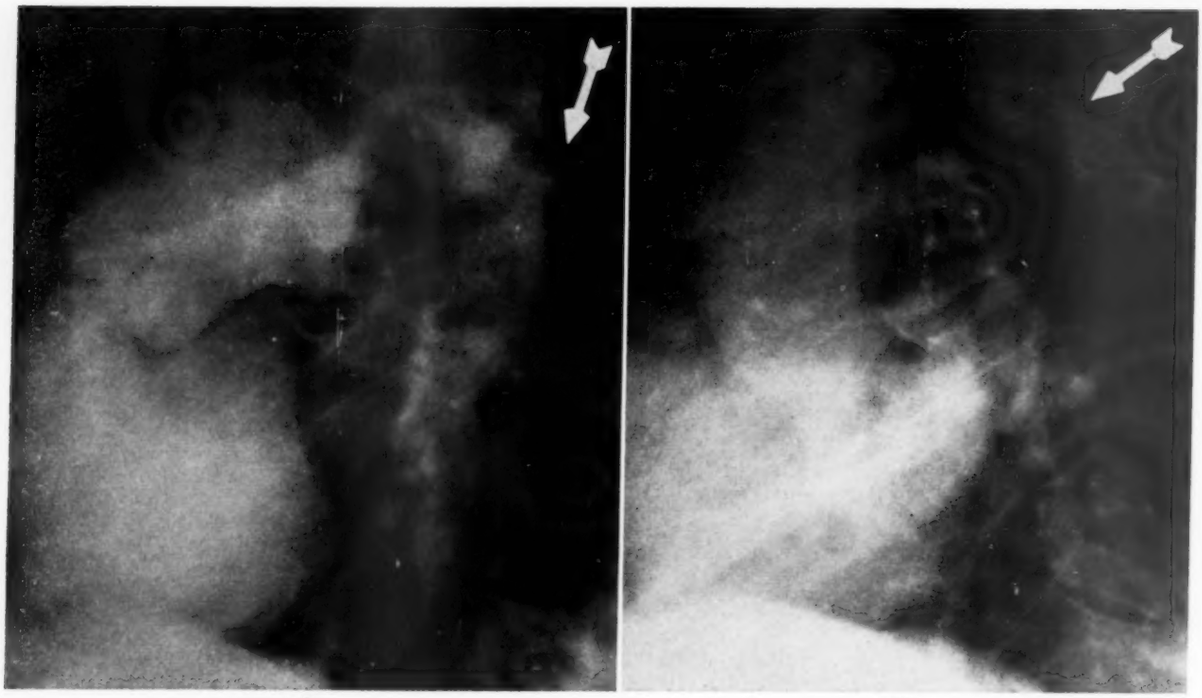
FIG. 1E. Tracing of Figure 1D.

gram of the chest showed clear lung fields, moderate enlargement of the heart and pulmonary artery, and extensive calcification of the pulmonary artery and its right and left branches. The electrocardiogram showed normal sinus rhythm, right axis deviation, and right ventricular hypertrophy. Blood cultures were sterile. The patient became afebrile after three days; four days later she was discharged.

On December 19, 1959, she had sudden increase in dyspnea and was discovered to have atrial fibrillation. Physical examination disclosed marked cyanosis, more evident below the mid-thorax. Clubbing of the fingers was mild; clubbing of the toes was conspicuous. A long, loud, rough systolic murmur obscuring the first heart sound was best heard in the second left intercostal space, and was widely transmitted. A loud, blowing early diastolic murmur was also present in the same area. Atrial fibrillation with ventricular rate of 120 per minute with a large pulse deficit was present. The blood pressure was 120/60 mm. Hg. The veins of the neck were engorged and the liver edge was palpable 3 cm. below the left costal margin. There was no orthopnea and the lungs were clear.

Laboratory data disclosed the following: hemoglobin 19.9 gm./100 cc.; erythrocytes 5.9 million/cu. mm.; hematocrit 61 per cent. A roentgenogram of the chest showed enlargement of the heart and prominence of the aortic knob and pulmonary artery. There was striking calcification in the wall of the pulmonary artery and of the right and left pulmonary arterial branches. A rim of calcification was also present in the wall of the aortic knob and along the outer margin of the tissues below the aorta and pulmonary artery. (Figs. 2A and 2B.) The electrocardiogram showed

FIG. 1F. When the left ventricle is opacified, the pulmonary artery is reopacified, demonstrating the left-to-right shunt via a patent ductus arteriosus.



1G 1H

FIG. 1G. Lateral angiocardiogram showing opacification of the descending aorta (arrow) at the time of pulmonary arterial filling.

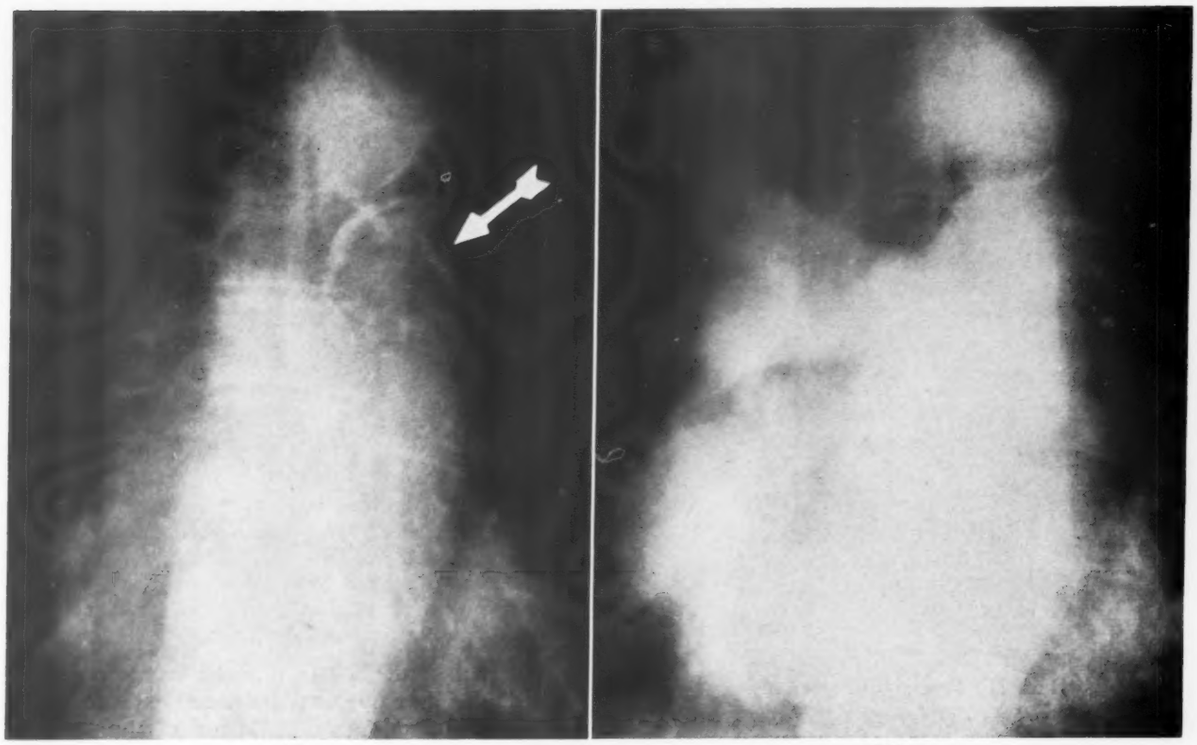
FIG. 1H. When the ascending aorta is filled there is reopacification of the left pulmonary artery (arrow).

atrial fibrillation, right axis deviation, and right ventricular preponderance. Angiocardiography performed on December 23, 1959, showed a normal-sized right atrium, a huge right ventricle, and marked widening of the pulmonary artery and its branches. Opacification of the aortic knob and descending aorta was seen at the time of opacification of the left pulmonary artery. The opacified ductus, measuring 24 mm. at its widest diameter, was clearly seen just above the left pulmonary artery. (Figs. 2C, 2D, 2E and 2F.)

FIG. 2A. Case II. Frontal teleroentgenogram showing marked enlargement of the heart, pulmonary artery and plethoric lungs. Calcifications around the left branch of the pulmonary artery, the tissues between the aortic knob and pulmonary artery, and aortic knob are evident.

The patient improved on digitalis therapy. On the sixth hospital day her heart reverted to regular sinus rhythm with striking diminution in cyanosis; the blood pressure rose to 150/70 mm. Hg. Subsequently, there were recurrences of atrial fibrillation with an increase in cyanosis and dyspnea. She died suddenly on June 22, 1959. Autopsy performed by the medical examiner was summarized as follows: persistent ductus arteriosus 1 cm. in diameter with calcification of the wall; ventricular septal defect 4 mm. in diameter; cardiac hypertrophy; arteriosclerosis of the pulmonary artery with ulceration and calcification, and multiple thrombi in both branches of the pulmonary artery.

CASE III. A thirty-nine year old woman (No. 194,909) had had heart disease since childhood. Exertional dyspnea began early in life and gradually progressed. A heart murmur was heard by several physicians. In 1950 during the delivery of a full term, normal child she became cyanotic and required



2B 2C

FIG. 2B. Overpenetrated frontal roentgenogram shows the calcification of the left pulmonary artery, ductus (arrow) and aortic knob.

FIG. 2C. Frontal angiocardiogram showing enlargement of the right atrium, ventricle, pulmonary artery and branches. The patent ductus arteriosus and the opacified aortic knob and descending aorta demonstrate reversal of blood flow through the ductus.

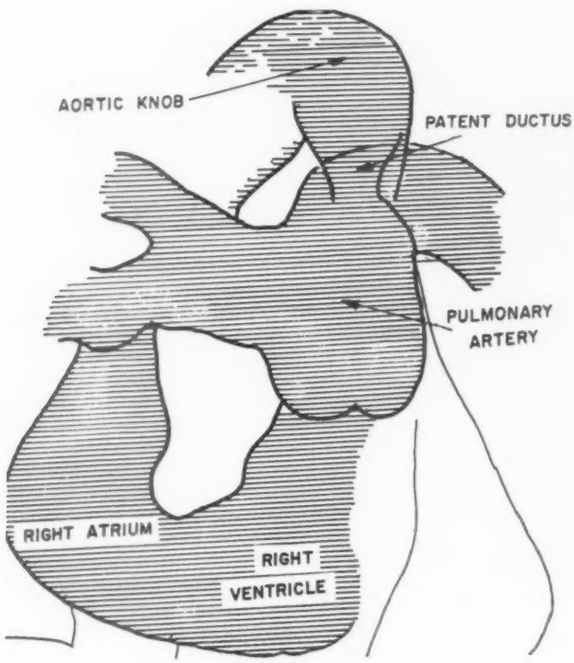


FIG. 2D. Tracing of Figure 2C.

FIG. 2E. Lateral angiocardiogram also shows the enlarged right heart chambers, pulmonary arterial system and the reversed blood flow through a patent ductus arteriosus.

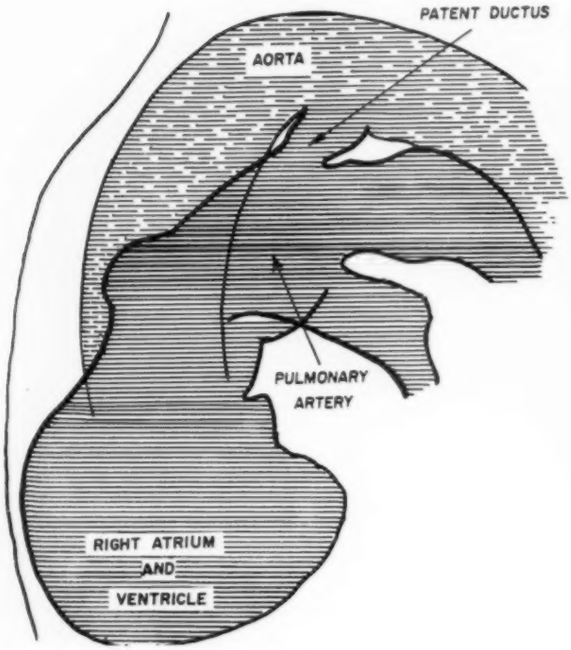


FIG. 2F. Tracing of Figure 2E.

oxygen. In 1952 she noted cyanosis. After a roentgenogram of the chest in 1955, admission to the Bethesda Naval Hospital was advised. A diagnosis of patent ductus arteriosus was made after cardiac catheterization, but surgery was not advised because of severe pulmonary hypertension. On April 28, 1958, she was admitted to the U. S. Naval Hospital, St. Albans, New York. She had no respiratory distress but appeared cyanotic; the lungs were clear. At the second and third left sternal cartilages, a moderately loud systolic and a somewhat louder blowing early diastolic murmur were heard. The second pulmonic sound was accentuated and split. The blood pressure was 120/60 mm. Hg. There was marked clubbing and cyanosis of the fingers and toes. The hemoglobin was 16.8 gm./100 cc. and the hematocrit was 63 per cent. The electrocardiogram showed right axis deviation and right ventricular preponderance. Only the pulmonary arterial pressure (126 mm. Hg) was recorded during cardiac catheterization on April 30, 1958.

She was readmitted on January 5, 1959, because of persistent edema of the ankles, dyspnea, orthopnea and severe cyanosis. Physical examination revealed a thin, delicate woman with respiratory distress. Cyanosis was moderate in the lips and nail beds, and intense in the legs and toe nails. Clubbing of the fingers and toes was also present but more marked in the latter. The jugular and peripheral veins were distended; the lungs were clear. The heart was enlarged, and the heart sounds were of good intensity. The second pulmonic sound was louder than the aortic and was split widely. There was a short, moderately loud systolic murmur heard best along the left sternal border, but a diastolic murmur was not heard. The liver was non-tender and extended 5 cm. below the costal margin. Edema of the legs was marked.

Laboratory data showed hemoglobin 19 gm./100 cc. with a hematocrit of 60 per cent. A roentgenogram of the chest revealed marked enlargement of the heart.

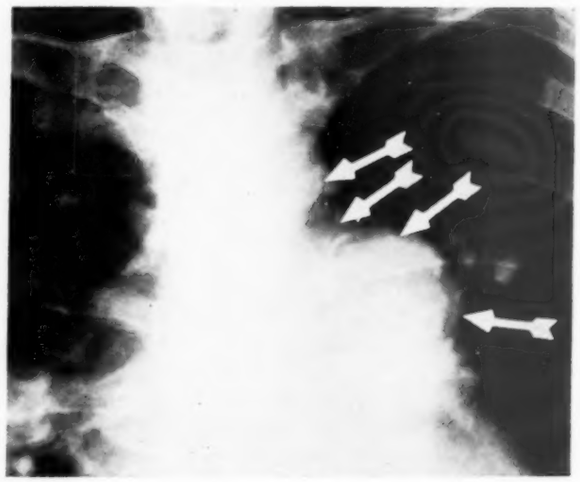


FIG. 3A. Case III. Frontal teleroentgenogram demonstrating cardiac enlargement, pulmonary arterial enlargement and plethoric lungs. The pulmonary artery calcification is marked by the lower arrows. The upper arrows point to the calcified ductus and aortic knob.

FIG. 3B. Lateral roentgenogram shows the enlargement to be predominantly of the right heart chambers. Note the calcification of the pulmonary artery.

FIG. 3C. Left anterior oblique angiocardiogram revealing right ventricular and pulmonary artery enlargement with opacification of the descending aorta via a ductus.

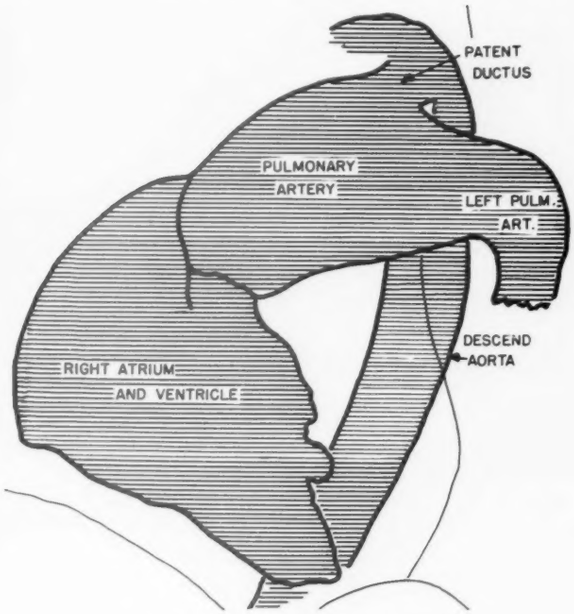


FIG. 3D. Tracing of Figure 3C.

The pulmonary artery segment was also markedly enlarged and there was prominent calcification of the walls of the pulmonary artery. (Figs. 3A and 3B.) The angiocardiogram showed marked enlargement of the pulmonary artery with reversal of blood flow through a patent ductus arteriosus. (Figs. 3C and 3D.) The electrocardiogram showed right ventricular hypertrophy and right axis deviation. Blood volume studies were as follows: whole blood volume 116 ml./kg. (normal 73 ± 4); plasma volume 37 ml./kg. (normal 42 ± 2); red cell volume 79 ml./kg. (normal 31 ± 2).

With the administration of digitalis and diuretics, and restriction of salt, diuresis resulted and peripheral edema decreased. Cyanosis, however, increased. On the ninth hospital day sudden severe dyspnea associated with cough and fever developed. The dyspnea and cyanosis increased and the patient died.

Postmortem examination revealed the weight of the heart to be 490 gm. There was marked right ventricular hypertrophy, the walls measuring 1.5 cm. in thickness; the left ventricular wall ranged from 0.8 to 1.2 cm. The heart valves were intact. The aorta at its origin measured 6.3 cm. in circumference, and the pulmonary artery 11 cm. There was minimal atherosclerosis of the intimal surfaces of the aorta. A patent ductus arteriosus measured 1 cm. in internal diameter and 0.9 cm. in length. (Fig. 3E.) On the aortic side of the ostium of the ductus there was marked atherosclerosis and calcification. (Fig. 3F.) The main pulmonary artery was severely involved with atherosclerosis, most prominently at the area opposite the patent ductus. Just above this area there was also a firmly attached thrombus measuring 0.4 by 0.3 cm. at the base extending into the left pulmonary artery for a distance of 11 cm. and into the right pulmonary artery for a distance of 6 cm. It occluded approximately 50 per cent of the lumina of the pulmonary arteries. The smaller pulmonary vessels were markedly engorged with blood. Some of the smaller pulmonary arteries showed atherosclerosis. Microscopic studies of the lungs showed varying degrees of atherosclerosis of the larger and medium sized arteries with thickening of the vessel walls. There was also intimal fibrosis, vacuolization and lipoidosis; in the larger vessels there were foci of calcification.

CASE IV. A thirty-four year old woman (New York Hospital No. 555,545) was first seen in June 1950 complaining of malaise, fever and cough. Although she did not have cyanosis at birth, heart murmurs had been noted at an early age, and she had had five episodes of pneumonia before the age of seven years. She had had a long-standing curvature of the spine with consequent asymmetry of the thoracic cage. Dyspnea on exertion was first noted in 1945 and persisted. On the first admission she was febrile (39°c.) and had a rapid pulse of 106 with respirations of 36 per minute. She was acutely ill, poorly developed and nourished, and had a "child-like" facies. There was moderate cyanosis of the lips and nail beds; she coughed frequently but was able to lie flat in bed. Severe kyphoscoliosis with deformity of the thorax and enlargement of the heart were present. A loud, widely transmitted systolic murmur, and a short blowing early diastolic murmur was heard over the third left interspace. The pulmonic second sound was strongly accentuated and many medium rales were heard over the left mid-lung posteriorly. The fingers were moder-

3E 3F

FIG. 3E. Photograph of heart with arrow pointing to unopened short wide ductus between dilated pulmonary artery below and small aorta above.

FIG. 3F. The aortic end of the ductus. Note the calcifications (arrow).

ately clubbed and the hemoglobin was 18 gm./100 cc. with erythrocytes 6.7 million/cu. mm. Blood cultures were sterile. The roentgenogram showed moderate cardiac enlargement. The electrocardiogram showed normal sinus rhythm, right axis deviation, and right ventricular hypertrophy. Angiocardiography on August 24, 1950, showed that the right ventricle, pulmonary artery and its principal branches were all huge. The descending aorta was filled from the pulmonary artery. (Figs. 4A and 4B.) Antibiotics failed to reduce the fever. She finally became afebrile on the forty-first hospital day and was discharged after sixty-nine days.

Cardiac catheterization on a subsequent admission (February 1951) showed the blood oxygen content, in volumes per cent, to be as follows: femoral artery 19.6; left pulmonary artery 15.8; right ventricle (outflow) 14.6; right ventricle (inflow) 14.1; right atrium 14.4; superior vena cava 14.8; arterial O_2 capacity 24.5 volumes per cent and arterial O_2 saturation 80.8 per cent. Pressures in mm. Hg were: femoral

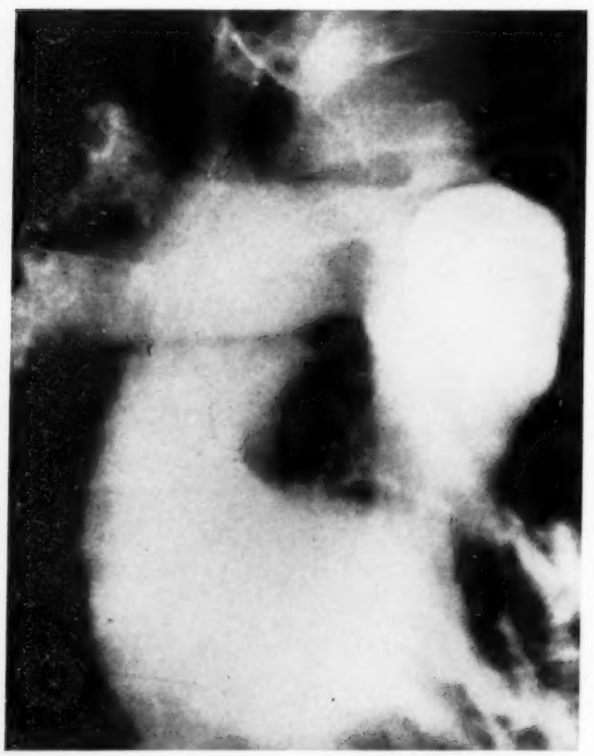


FIG. 4A. Frontal angiocardiogram with marked right ventricular and pulmonary arterial enlargement. The descending aorta is opacified via a patent ductus arteriosus.

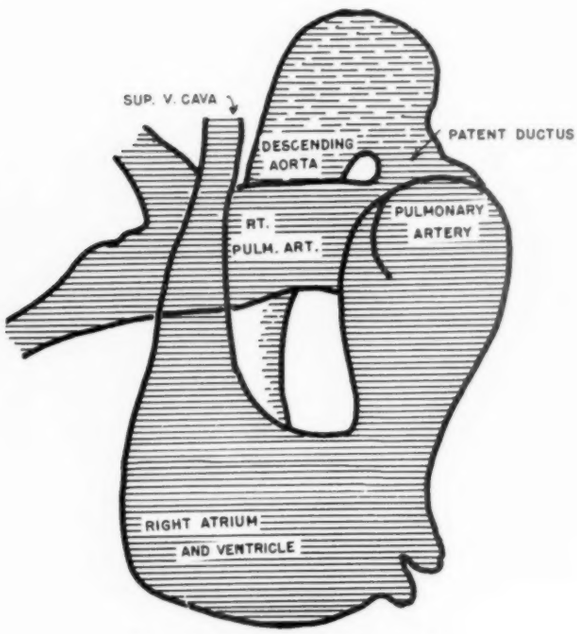
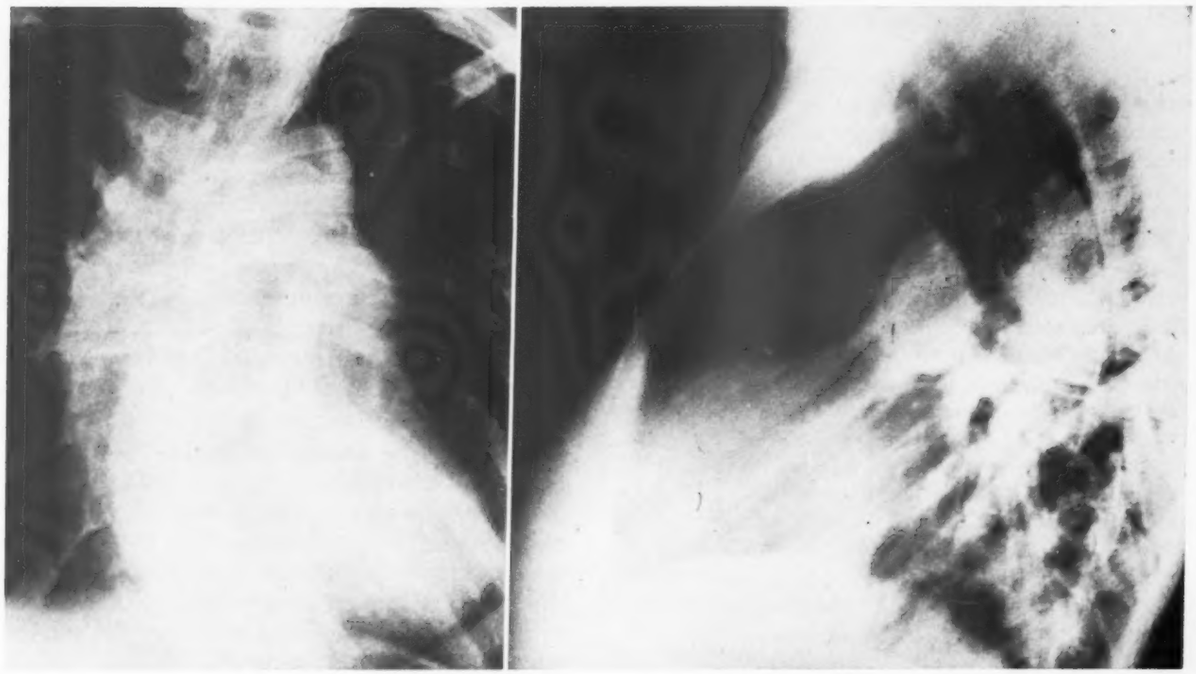


FIG. 4B. Tracing of Figure 4A.



4C 4D

FIG. 4C. Frontal teleroentgenogram showing scoliosis of the spine, cardiac and pulmonary enlargement.

FIG. 4D. Lateral roentgenogram revealing the calcified left pulmonary artery.

FIG. 4E. Photograph of the heart showing wide patent ductus between dilated pulmonary artery (below) and aorta (above). Note thick right ventricular wall.

artery (mean) 78; "pulmonary capillary" 8; pulmonary arterial 116/80 (mean 97); right ventricle 125/10; and right atrium 3.

In February 1957, during the seventh month of her first pregnancy, the patient was readmitted because of hemoptysis. Three days later she went into labor spontaneously and was delivered of an infant (weighing 500 gm.) who survived for one hour. She was readmitted on December 9, 1959, in the eighth month of a second pregnancy, because of hemoptysis. The

FIG. 4F. Pulmonic end of ductus (arrow) with detail of calcific deposits. Below, right and left pulmonary arteries.

pulse was 96 per minute and regular; the blood pressure was 140/80 mm. Hg. There was no respiratory distress. The venous pressure was 110 mm. saline. The lungs were clear. The second pulmonic heart sound was accentuated. A moderately loud, early, blowing diastolic and an inconstant systolic murmur were present in the second left intercostal space at the left sternal border. A presystolic gallop was also present. The roentgenogram of the chest showed enlargement of the heart and a dilated pulmonary artery with a rim of calcification in the wall. (Figs. 4C and 4D.) The hematocrit was 41 per cent. The electrocardiogram showed regular sinus rhythm, rate 83, right axis deviation, and right ventricular hypertrophy. She was asymptomatic until December 14, 1959, when premature spontaneous delivery occurred. The postpartum course was uneventful. She then had bilateral tubal ligation under general anesthesia. The postoperative course was marked by fever, increasing cyanosis, and respiratory distress. On the third postoperative day she had acute dyspnea, intense cyanosis, and complained of chest pain. She subsequently went into shock and died.

Autopsy (No. 18,952), performed eighteen hours postmortem, revealed an enlarged heart (weight 410 gm.). The right ventricle was hypertrophied and measured 16 mm. in thickness across the base. The left ventricular wall measured 15 mm. The myocardium was grossly normal and all the valve cusps and leaflets were thin and delicate. The coronary arteries were widely patent, the foramen ovale was closed, and the interventricular septum showed no abnormalities. A patent ductus arteriosus measuring 13 mm. in diameter and 20 mm. in length arose 4 cm. above the aortic valve in the arch of the aorta. (Fig. 4E.) The endothelium of the ductus and of the aorta and pulmonary artery adjacent to it was irregularly nodular and thickened with yellow calcified plaques. The walls of the pulmonary artery were irregularly thickened by yellowish atheromas. (Fig. 4F.) The aorta and great veins appeared normal. The lung parenchyma was grossly well aerated and non-nodular. Microscopic sections of the heart were normal. The lungs, however, showed some thickening of alveolar septa as well as congested blood vessels. Many small pulmonary arteries showed moderate to extreme intimal fibrocellular or hyaline intimal thickening; a few were completely occluded by the process.

Comments: The four patients, all women, aged forty-seven, sixty-five, thirty-nine and thirty-four, demonstrated the clinical and laboratory features of patent ductus arteriosus with reversal of blood flow. Cardiac murmurs were recognized early in childhood in each instance. Cyanosis developed late in life and was present in each patient when first observed. Dyspnea on exertion began early. Three patients (Cases I, II and IV) had recurrent hemoptysis. All were poorly developed and two (Cases III and IV) had deformities of the thoracic cage, findings previously noted in this syndrome [*11,12*]. Digital clubbing, as well as cyanosis, were present in all, and in three patients they were more marked in the lower extremities. Deeper cyanosis of the left hand, a sign associated with reverse shunt [*8,13*], was not noted in any of our patients.

All patients had pulmonary hypertension and right ventricular hypertrophy. In no instance was a continuous murmur such as characterizes the isolated patent ductus heard, but instead a loud systolic murmur, an accentuated pulmonic second sound, and the diastolic murmur of pulmonic insufficiency. Polycythemia of severe degree was present in all patients. In Case I it had led to a mistaken diagnosis of polycythemia vera and treatment with radioactive phosphorus. The electrocardiogram provided confirmatory evidence of right ventricular hypertrophy in all the patients. One (Case I) showed, in addition, the RSR'-V_1 pattern associated with hypertrophy of the right ventricular outflow tract [*14*]. Cardiac catheterization in three patients revealed pulmonary pressures in the range of the systemic pressures and low arterial oxygen saturation typical of the anomaly. The catheter, however, passed from the pulmonary artery to the aorta in only one patient (Case I).

Calcification of the wall of the pulmonary artery was clearly demonstrated in the chest roentgenograms of all the patients. (Figs. 1A and 1B; 2A and 2B; 3A and 3B; and 4C and 4D.) Although visible in the frontal view, it was better delineated in the lateral view in which a curvilinear density outlined the wall of the pulmonary artery. (Figs. 1B, 3B, and 4D.) In one patient (Case IV) the thick line of calcium outlined the entire cross section of the arterial wall. (Fig. 4D.) In this case the lateral edge of the ductus was marked by a thin calcific density. (Fig. 4D.) In two others (Cases I and II) both walls of the calcified ductus could be seen. (Figs. 1A and 2A.) The wall of the aortic knob adjacent to the ductus was also marked by a curvilinear calcific density. (Figs. 1A; 2A and 2B; 3A; and 4C.)

Angiocardiography was of considerable diagnostic value. It demonstrated the presence of reversal of shunt by revealing the simultaneous early opacification of the pulmonary artery, ductus, and descending aorta. (Figs. 1D, 1E, 1G, 2C, 2D, 2E, 2F, 3C, 3D, 4A and 4B.) The ductus itself was well visualized and its unusual

width, characteristic of patent ductus with reverse shunt, easily noted [*12,15*]. The unusual finding of early opacification of the ascending portion and arch of the aorta (Figs. 2E and 2F) in Case II can be explained by the presence, in this patient, of a ventricular septal defect in addition to the patent ductus. The coexistence of patent ductus arteriosus and ventricular septal defect has been previously noted [*15–18*].

COMMENTS

The most consistent pathologic finding in patients with patent ductus arteriosus with severe pulmonary hypertension and reversal of flow is the widespread sclerosis of the pulmonary arterial tree. In the major pulmonary arteries the lesions consist of atheromatous changes of varying degrees [*3,8,19,20,21*]. The atheromatous process in these large vessels is at times accompanied by deposits of calcium [*8,16,18,22*]. These calcific deposits may be heavy enough to be easily demonstrable in roentgenograms of the chest [*3,6,8,9*].

This association of calcification of the pulmonary artery and its main branches with the syndrome of patent ductus with reverse shunt has not been emphasized, although mentioned in the literature [*23,24*]. It seems of great significance that in no other form of congenital cardiopulmonary disease confirmed at autopsy has such calcification been reported. The calcium which is visible on the roentgenogram is found, at autopsy, to be deposited on the atheromatous intimal plaques. It is therefore an accompaniment of severe, usually diffuse atheromatous changes in these trunk arteries.

The incidence, degree and extent of pulmonary atheroma in patients with patent ductus with reversed shunt vary widely [*15*]. The same may be said for calcific atheroma. Age is important, for in general the older the patient the more severe the degree of atheroma and the more extensive its distribution. This is in keeping with the findings of Brenner [*25*] and of Costa [*26*], that the incidence of sclerosis of the large pulmonary arteries increases with age even in the absence of other contributing factors. Notable exceptions may be found, however, for Damman [*10*] reported finding calcific atheroma at autopsy of a four and a half year old girl with "reverse patent ductus." The other patients with this syndrome, reported in the literature as showing extensive pulmonary artery calcification, were aged twenty-five [*3*], twenty-nine [*8*], thirty-five [*9*] and fifty-one [*6*]. On the other hand, no calcification was apparent in patients with reverse ductus aged forty-two [*20*], thirty-six [*27*] and fifty-eight [*15*].

It is widely assumed that pulmonary artery sclerosis is the result of severe, prolonged pulmonary hypertension from any cause [*8,25*]. Heath and Whitaker [*28*] found a close relationship between pulmonary arterial pressure and histologic changes in the pulmonary arterial system. On this premise it is not surprising to find a high incidence of severe sclerosis in patent ductus with reverse shunt, for pulmonary hypertension to systemic levels is requisite for the diagnosis. It is difficult to explain the lack of a parallel incidence of calcific atheroma in the other defects attended by severe pulmonary hypertension. It may well be that the location of the shunt is an important factor in the production of severe atheroma, and the determining etiologic factor in the formation of calcific deposits. The exact localization of the calcium plaques, where present, lends weight to this hypothesis, for the thickest deposits are almost invariably found in the portions of the pulmonary artery either adjacent or opposite to the patent ductus. These are areas exposed to the additional stress of great blood turbulence. It is the only factor which is present in reverse shunt at the ductus level and absent when the shunt is at other anatomic levels.

Calcifications associated with the more common isolated patent ductus arteriosus are confined, when present, to the ductus itself and to the adjacent portions of the aorta [*29–34*]. It occurs most frequently in the older patients [*33*]. Calcification of the pulmonary artery or of its main branches, however, has never been observed in patients with isolated ductus irrespective of age. Both Bain [*31*] and White [*34*] report individual patients aged eighty-five and sixty-six, respectively, with isolated persistent ductus. At necropsy extensive calcification of the ductus and of the aorta was found, but in each instance the pulmonary arteries were free of atheroma. In a pathologic study of the pulmonary vasculature in congenital cardiac defects, Welch and Kinney [*35*] found no greater incidence of pulmonary atherosclerosis in patients with isolated patent ductus than in a control group of comparable age.

SUMMARY

Calcification of the pulmonary artery in a patient with enlargement of the right ventricle

and main pulmonary arteries constitutes dependable evidence of patent ductus arteriosus with reversal of blood flow. In a series of four women with this syndrome, in three of whom the diagnosis was confirmed by postmortem examination, the conventional roentgenogram showed calcification of the pulmonary artery and ductus providing a clue for the diagnosis. Search of the literature failed to reveal any other cardiopulmonary condition which produced this finding. Accordingly, the presence of calcification in the wall of the pulmonary artery and/or its main branches strongly suggests the diagnosis of patent ductus with reversed shunt. Appropriate confirmatory procedures such as determinations of blood oxygen in the upper and lower extremities, cardiac catheterization, and angiocardiographic studies may then be promptly undertaken.

Acknowledgment: We are indebted to Dr. Harry Weintraub for follow-up data and to Dr. William J. Noble for making available the cardiac catheterization data in Case I; to Dr. Dominick J. Di Maio, Deputy Medical Examiner, City of New York, for the summary of the autopsy of Case II; and to the late Capt. Charles Gantenlaub, MC, USN for permission to include Case III.

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Reviews

Syncope*

Physiological Considerations and an Analysis of the Clinical Characteristics in 510 Patients

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SYNCOPE, strictly speaking, can be defined simply as temporary loss of consciousness. This automatically excludes various phenomena loosely categorized as syncopal reactions, such as dizziness, lightheadedness, pallor, cold sweats, weakness and faintness, and sometimes referred to as neurocirculatory asthenia, vasomotor instability and vasovagal reactions. It is true that many of these phenomena often accompany syncope, but they may occur by themselves, so that more correctly these should be referred to as autonomic reactions.

To convey greater meaning, more should be added to the definition of syncope than simply "loss of consciousness." Thus it could be said that syncope is a symptom of a large variety of disorders, having certain precipitating factors, warning signs, characteristic manifestations during the period of unconsciousness, and certain postsyncopal residua. It is in reality a reflection of an underlying physiological or pathological disorder. Although of critical importance, the history obtained is often grossly inadequate, and not just because the patient is unable to supply the information. Many examiners inquire primarily into the syncopal episode itself—whether or not there were convulsions, urinary or fecal incontinency, biting of the tongue, sweating or pallor. Often overlooked is the amount of fatigue, the lack of food, the degree of emotional tension, the position of the body, the activity the body was engaged in (such as exertion or sudden change of position), the environmental temperature, a recent illness and previous known disease. What was the nature of the immediate warning symptoms—were there cardiac irregularities, angina, aura of any kind, paresis or incoordination, paresthesias, vertigo or involuntary movements—and what was the duration of the warning symptoms? Indeed, were there any warning symptoms at all? During the syncopal period, what was the color of the skin, the character of the respirations and heart beat, and what was the duration of the unconscious period? In the postsyncopal period was there any confusion, and for how long did the patient sleep, or were there any other residua?

It becomes apparent that a great deal is involved in the investigation of loss of consciousness; it requires not only an orderly classification, but also an understanding of basic mechanisms. The present study is, however, a clinical one based on an analysis of approximately 500 cases of syncope taken from the records of the Cleveland Clinic between the years 1945 and 1957. This approach would have little merit, however, without some consideration of the basic physiologic changes involved and for this reason, some review of the problem is in order.

BASIC PHYSIOLOGY OF SYNCOPE

The various fundamental mechanisms causing loss of consciousness are illustrated in Figure 1. It is apparent that unconsciousness can be brought about in one of three ways: (1) *as a result of cerebral ischemia*, either localized

* This study was conducted while the author was a Fellow in Medicine at the Cleveland Clinic, Cleveland, Ohio, the last ten months of which were Air Force sponsored. The contents of this paper reflect the personal views of the author and should not be considered as representing official Air Force policy.

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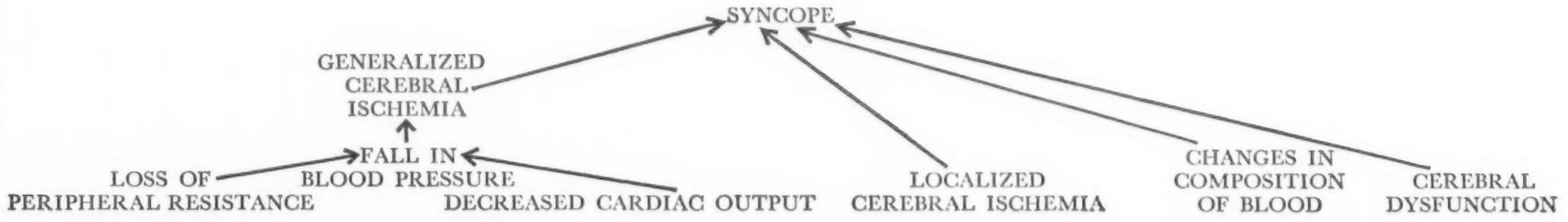

A. *Active loss (reflex)*

1. Vasovagal syncope
2. Carotid sinus syncope
3. Hyperventilation syncope
4. Cerebral reflexes
   a) Syncope due to cough, positive pressure breathing, negative G forces
5. Intracardiac reflexes
   Syncope due to aortic stenosis, aortic insufficiency
6. Coronary reflexes
   Myocardial infarction
   Angina pectoris
7. Pulmonary reflexes
   Cough syncope
   Positive pressure breathing
   Pulmonary embolism
   Pulmonary hypertension
8. Aortic reflexes
   Dissecting aneurysm

B. *Passive loss*

1. Orthostatic hypotension (transient)
   Convalescence, reaction to drugs, post-sympathectomy, physical exhaustion, starvation, positive G, positive pressure breathing, prolonged standing, etc.
2. Chronic orthostatic hypotension
   a) Idiopathic
   b) Secondary—central nervous system disease, etc.

A. *Cardiac standstill*

1. Vasovagal (cardioinhibitory)
2. Carotid sinus (cardioinhibitory)
3. Adams-Stokes attacks

B. *Decreased stroke volume*

1. Aortic stenosis
2. Myocardial infarction
3. Angina pectoris
4. Cardiac arrhythmias
5. Aortic insufficiency and mitral stenosis (rare)

C. *Extracardiac causes*

1. Pulmonary hypertension
2. Positive pressure breathing
3. Cough syncope
4. Valsalva maneuver
5. Positive G forces

A. *Cerebral vascular disease*

1. Arteriosclerosis
2. Thrombosis

B. *Cerebral vasospasm*

1. Secondary to embolism or thrombosis
2. Migraine
3. Hypertensive encephalopathy
4. Hyperventilation syncope
5. Neurocirculatory collapse
6. Carotid sinus syncope (central type)

A. *Hypoxia*
1. High altitude
2. Congenital heart disease

B. *Hypocapnia*
1. Hyperventilation

C. *Hypercapnia*
1. Space flight
2. Asphyxia

D. Hypoglycemia

E. Nutrition deficiency

A. Epilepsy
B. Carotid sinus syncope (central form)
C. Hysteria
D. Trauma
E. Brain tumor

FIGURE 1.

or generalized; (2) *as a result of a change in the composition of blood* or (3) *as a result of a reflex cerebral dysfunction.*

Generalized Cerebral Ischemia

Sudden Active Loss of Peripheral Resistance. Generalized cerebral ischemia follows a rapid drop in blood pressure and is seen with sudden active or passive loss of peripheral resistance. Also it may be secondary to a reduction in cardiac output as a result of cardiac standstill, a decreased stroke volume, or it may stem from extracardiac causes. Of all these, however, active loss of peripheral resistance is the most frequent mechanism involved. Barcroft et al. [*1*] have demonstrated, in subjects with venesection plus strapping to a tilt table, an initial rise in total peripheral resistance and heart rate, while the blood pressure, right atrial pressure and cardiac output fall to some degree. Shortly prior to the faint, cardiac output and right atrial pressure begin to rise, and do not fall during the actual loss of consciousness. Total peripheral resistance, heart rate and blood pressure fall precipitously, however, while forearm muscle flow increases considerably through evident vasodilatation. The failure of the cardiac output to fall in the face of a marked bradycardia and fall in peripheral resistance at the onset of a faint has been confirmed by other workers [*2,3*]; in addition, there is no significant change in the stroke volume, circulation time or venous pressure [*3*]. That the bradycardia is not an essential part of the picture is shown by the prior administration of atropine. This abolished the bradycardia but not the loss of consciousness [*3,4*]. Warren et al. [*2*] believe that circulatory collapse is primarily a sudden reflex loss of peripheral resistance and is not secondary to the decrease in venous return. The associated symptoms of bradycardia, weakness, sweating, nausea and pallor are the result of intense autonomic nervous system stimulation, as is the vasodilatation and fall in blood pressure, rather than being secondary to the hypotension. Many of these changes persist for some time after the blood pressure has returned to normal, and in some forms of syncope these phenomena are not present, i.e., Adams-Stokes' syndrome and postural hypotension. There is some evidence to show that a few of the associated signs are hormonal in origin, in particular, Pitressin® [*5,6*]. For example, the administration of Pitressin will duplicate many of the changes seen in syncope, such as nausea, pallor and the urge to defecate; indeed, an antidiuretic hormone has been demonstrated in the urine of subjects who lose consciousness. Other areas in which there is vasodilatation coinciding with the loss of consciousness include chiefly the splanchnic and renal vascular beds [*7,8*]. Thus the precipitous shunting of large quantities of blood through the muscle, splanchnic and renal beds is reason enough for the marked drop in blood pressure to values as low as 40 mm. Hg or even less, with resulting cerebral ischemia.

Vasovagal syncope: Of the various types of fainting caused by a sudden reflex loss of peripheral resistance, the most common is the vasodepressor form of vasovagal syncope. This was originally described by Lewis [*9*] and is more frequent than all other forms of syncope combined. There are two kinds—the vasodepressor and the cardioinhibitory; the latter is sometimes referred to as a reflex Adams-Stokes syndrome and is less frequent. Only the former will be considered at this point. A list of all the things which can precipitate an episode of vasovagal syncope would be too long to include here. Some of the more important ones will be detailed later under a consideration of the clinical characteristics; however, they have in common pain, fear or other emotional stress, fatigue, hypoglycemia and blood loss. Since intense autonomic nervous system stimulation precedes the fall in blood pressure, the patient has a relatively long warning period, the duration depending upon the nature and intensity of the stimulus. In many instances an attack can be aborted by assuming the recumbent position, which helps counteract the pooling effect of gravity to some degree. Thus the patient might have as long as several minutes or as short a time as ten to twenty seconds before loss of consciousness supervenes.

Engel [*10*] has advanced the interesting concept that this form of syncope is a sort of general response to fear or injury. It will be recalled that many of the physiological changes seen in fainting are commonly seen with fear; but, as Engel points out, flight is often not possible. Although the circulatory preparation for flight takes place with an increase in blood flow to the muscle bed, there is no compensatory increase in muscular activity to aid in venous return, nor does the cardiac output increase. Thus blood pressure falls and the person faints. While undoubtedly this is an important factor in some instances there are other things which must be accounted for, namely, the failure of the cardiac output to

fall just prior to the loss of consciousness. Also, the administration of atropine fails to prevent unconsciousness even though it does prevent the bradycardia.

A more simple explanation for the loss of consciousness is evident. The sudden loss of peripheral resistance may cause the blood pressure to drop to levels as low as 35 to 40 mm. Hg, even before a decrease in venous return takes place. A simple calculation shows that the height of a column of blood having a hydrostatic pressure of 40 mm. Hg is approximately 54 cm. The average distance from the heart to the brain is about 45 cm., the hydrostatic equivalent of which is 33 mm. Hg. In other words, approximately 33 mm. Hg pressure is needed just to overcome the force of gravity. The remaining few millimeters of pressure is simply not enough to perfuse the brain with blood. Since only five to ten seconds of total ischemia is necessary for unconsciousness, fainting can very readily and rapidly ensue. This explains also the rapid return of consciousness in the recumbent position and its effective prevention, in this kind of syncope, by the administration of epinephrine.

Carotid sinus syncope: There are three types of carotid sinus syncope, as originally described by Weiss et al. [*11–13*], all brought about by hypersensitivity of the carotid sinus without associated hyperactivity of other portions of the autonomic nervous system. (1) *Cardioinhibitory:* In this a reflex vagal inhibition of the heart takes place, causing a fall in blood pressure. This can be prevented by the administration of both atropine and epinephrine. (2) *Vasodepressor:* Stimulation of the carotid sinus causes a fall in blood pressure which is independent of any change in heart rate and which is abolished by the administration of epinephrine only. (3) *Central type:* Loss of consciousness occurs as early as three to four seconds after stimulation of the carotid sinus, the other forms taking two to three times as long. There is no significant change in the heart rate or blood pressure and this form is not abolished by the administration of atropine or epinephrine. Only the vasodepressor carotid sinus syncope will be discussed at this point.

The vasodepressor form is almost identical with that of vasovagal syncope and most everything said about the latter undoubtedly applies to the former. Patients with vasovagal syncope, however, do not exhibit hypersensitivity of the carotid sinus. The main difference is that this, as well as the other two types, can be reproduced with pressure upon one or both of the carotid sinuses. There are other dissimilarities. It occurs more often in the sitting position and can occur in the recumbent position; it is more often seen in the older age groups, particularly those with cardiovascular disease. This is not to say that vasovagal syncope does not occur in older patients; it does, and not uncommonly; however, it is often independent of the associated disease. Weiss [*12*] has demonstrated that stimulation of the carotid sinus in normal subjects causes no response in 30 per cent and a fall in blood pressure of 10 mm. Hg or less in the remainder. However, in patients with hypertension or arteriosclerosis, carotid sinus massage created a fall in blood pressure of 30 to 40/18 to 25 mm. Hg and a drop in heart rate of 8 to 16 beats per minute in approximately 80 per cent. Hypersensitivity of the carotid sinus reflex may be seen also in patients with inflammatory or neoplastic disease of the neck, arteriosclerotic aneurysmal dilatation of the sinus, biliary tract disease and following the use of certain drugs, in particular digitalis [*14*]. Thus, not only may there be hypersensitivity of the sinus but of the end organ as well. This is one of the objections to the prophylactic use of preoperative digitalization in which there is apt to be endotracheal anesthesia and extensive instrumentation.

There are a number of other conditions which may induce a vasodepressor type of syncope; indeed, the possibility is not at all remote that these represent some of the fundamental mechanisms in the development of vasovagal syncope. These will now be discussed.

Hyperventilation syncope: Although the hyperventilation syndrome is extremely common, loss of consciousness resulting from overbreathing is rare. In a series of 165 subjects who were voluntarily hyperventilated to the point of muscular incoordination, none fainted [*15*]; however, susceptible people require much less overbreathing to develop symptoms than others [*16,17*]. There are several possible mechanisms whereby loss of consciousness can occur. These can best be evaluated when the various changes brought about by hyperventilation are considered. Considerable increase in peripheral blood flow can occur with both splanchnic and muscle vasodilatation and resulting hypotension [*18–20*]. Electrocardiographic changes occur which have been interpreted as evidence of myocardial ischemia [*21–23*]; in fact, rapid reduction in alveolar P_{CO_2} may produce arrhythmias in dogs

(including ventricular fibrillation) as well as severe hypotension [*24*]. Comparatively mild hyperventilation brings about a reduction in cerebral blood flow by as much as 35 per cent [*25,26*], and is apparently due to cerebral vasoconstriction [*27–30*]. In addition, hypocapnia, as is well known, shifts the oxygenoglobin dissociation curve to the left. The resulting increased affinity of hemoglobin for oxygen impairs to some degree the release of oxygen to the brain cells. Slowing of the electroencephalogram occurs of a degree consistent with the level of consciousness [*31*]. Marked reduction in consciousness is associated with electroencephalographic waves of less than 5 cycles per second, a degree of slowing which may appear in hyperventilation. If hypoglycemia happens to be present also, the degree of slowing (and the level of consciousness) is even more marked [*32,33*]. Finally, hyperventilation characteristically appears in the nervous, tense, apprehensive subject who is classically a victim of vasovagal syncope.

Just which of these various factors is responsible for loss of consciousness is difficult to say, for it depends upon the rate and degree of hyperventilation, the age of the patient, his emotional makeup, and the presence of pre-existing disease, especially arteriosclerotic heart disease and cerebral arteriosclerosis. Functional impairment of performance does not usually occur until the arterial P_{CO_2} is around 25 mm. Hg [*34*], the normal being 40 mm. Hg. What is important, however, is that a single deep inspiration and expiration can reduce CO_2 tension by 7 to 16 mm. Hg [*31*]. Undoubtedly, a combination of factors comes into play, and inclusion of hyperventilation syncope in this particular group does not necessarily imply that reflex vasodilatation is the major factor causing loss of consciousness.

Aortic pressoreceptors: These are rarely involved in syncopal episodes but may be stimulated in dissecting aneurysm of the aorta and thus may account for some of the cases of loss of consciousness seen in the condition.

Reflexes from pulmonary vessels: Increased pressure in the pulmonary circuit causes a bradycardia and hypotension [*35,36*]. Two groups of receptors appear to be responsible: (1) increased pressure in the pulmonary conus causing a fall in heart rate, and (2) reflexes from the pulmonary veins brought about by elevation of the pulmonary venous pressure creating hypotension [*37*]. These reflexes may be of prime importance in the syncope associated with positive pressure breathing, pulmonary edema, congestive heart failure, coughing, pulmonary hypertension and pulmonary embolism. In the latter instance platelet breakdown with the liberation of serotonin may cause additional chemical stimulation [*38*].

Coronary reflexes: Certain chemicals cause bradycardia, vasodilatation and hypotension, as well summarized in previous reviews [*39–41*]. This is sometimes called the Bezold-Jarish reflex and is characteristically elicited by the veratrum alkaloids. It can occur only through the coronary vessels. Considerable more information is needed but they may be a factor in syncope associated with angina, coronary insufficiency, myocardial infarction and aortic stenosis. The stimulus may be ischemia, the liberation of serotonin from platelet breakdown [*42*], or tissue breakdown. Pressoreceptors in the coronary vessels have yet to be demonstrated.

Intracardiac reflexes: Baroreceptors have been demonstrated primarily in the right atria and left ventricle [*41,43*], and are activated by increased cardiac pressure. Exactly how this comes about is uncertain, i.e., whether diastolic size, diastolic filling pressure or systolic filling pressure. The reflex is mediated through the vagus nerve and results in bradycardia and hypotension, the former not being necessary for the development of the latter. Whether or not these reflexes play a role in the syncope seen in aortic stenosis, pulmonary hypertension, pulmonary edema and congestive heart failure is not certain.

Cerebral receptors: Baroreceptors stimulated by an increased intracranial pressure causing bradycardia and hypotension have been postulated [*44–46*]. Insufficient evidence exists to know whether these reflexes really are present and, if present, the degree of their sensitivity. Such reflexes could help explain the loss of consciousness seen with tussive syncope, hypertensive encephalopathy, positive pressure breathing, superior vena caval obstruction and negative G forces.

Passive loss of peripheral resistance: Fall in blood pressure with its resulting cerebral ischemia occurs as a result not only of active reflex loss of peripheral resistance but of a passive loss as well, and is seen in a distinct group of fainters who have orthostatic hypotension. The passive loss in peripheral resistance should not necessarily be considered synonymous with pooling for, as

will be seen, pooling is not the only mechanism and may not occur at all. It will be recalled that certain hemodynamic changes take place with the assumption of the upright position which teleologically are necessary to counteract the effects of gravity. Thus contraction of muscles in the lower extremities and their increase in tone aid in venous return. How important this is is evidenced by the known observation that prolonged strapping to a tilt table will result in spontaneous loss of consciousness in a certain number of subjects. Indeed, certain animals will die after prolonged suspension in the upright position. This same mechanism was undoubtedly the cause of death resulting from crucifixion in ancient times. Immobilization in the erect position following strenuous exertion is particularly apt to cause trouble. In a group of healthy young subjects following vigorous exercise and then strapped to a tilt table, orthostatic hypotension occurred in one half and loss of consciousness in one fourth [*47*].

Other mechanisms exist for the compensation of the upright position. Thus there is peripheral vasoconstriction and acceleration of the heart beat, and others less important [*48*]. Failure of these compensatory mechanisms can bring about a reduction of circulating blood volume and cardiac output by as much as 20 per cent [*49,50*] or more if unconsciousness occurs. Stead and Ebert [*51*] have pointed out that patients with postural hypotension do not pool more blood, but normal pooling causes an abnormal fall in blood pressure due to absence of reflex vasoconstriction.

Actually, there are several different kinds of orthostatic hypotension which can cause syncope. It may be temporary or chronic. Temporary orthostatic hypotension can occur in several distinct ways while the chronic form is idiopathic or secondary to other disease, in particular central nervous system disease.

Temporary orthostatic hypotension can occur (1) with primary failure of vasoconstrictor impulses to take place; on a mechanical basis; and (2) as a result of certain drugs. *Primary failure of vasoconstriction:* Classically, this is seen in the postoperative period following sympathectomy for hypertension. Most often some return of function takes place in a relatively short period of time. The most common form of syncope seen in this group is that which occurs in the convalescent period during recovery from many diseases in which prolonged recumbency is necessary. This is particularly noticeable in older patients, although poor muscle tone also may be a factor. Certain drugs, notably the ganglionic blockers such as hexamethonium, used in the treatment of hypertension, cause postural hypotension and syncope when administered in therapeutic doses; this being one of the major drawbacks to their use on an ambulatory basis. Fainting with prolonged standing in hot weather may be considered here although pooling of an abnormal amount of blood is probably of greater importance. In the same manner, the fainting seen in starvation and with physical exhaustion can be perhaps in part attributed to insufficient vasoconstriction, but abnormal pooling, decreased venous return and cardiac output can be considered of greater significance. *Drugs:* Certain drugs, especially those that are potent vasodilators, will cause hypotension in the erect position only, and occasionally also syncope. Amyl nitrite is a classic instance. In the recumbent position the oral administration of 3 gr. of sodium nitrite fails to cause any significant change; but if the subject is strapped to a tilt table, syncope takes place rapidly almost invariably [*52*]. The ganglionic blockers have already been mentioned. Emetine is another drug which will lead to postural hypotension [*53*] and there are undoubtedly many others.

Chronic orthostatic hypotension is usually secondary to some underlying disease of the central nervous system, but it also may be idiopathic. It is not infrequently seen in a mild form, manifested only by transient dizziness, and syncope secondary to this condition is relatively common. Unlike other forms of syncope in which active vasodilatation takes place, associated autonomic stimulation is not usually seen; and, as already pointed out, failure of vasoconstriction to take place rather than abnormal pooling of blood is the basic mechanism. Secondary orthostatic hypotension occurs in diabetic neuropathy, tabes dorsalis, multiple sclerosis, pernicious anemia, syringomyelia, peripheral neuritis and cerebral arteriosclerosis. In the idiopathic form there is the triad of anhidrosis, impotence and orthostatic hypotension in which syncope often occurs. The heart rate fails to change in the erect position while the cardiac output falls. The basic pathological lesion may lie in the hypothalamus, high in the spinal cord, or may be due to a central failure of the carotid sinus reflex [*54*].

To recapitulate thus far: One of the three basic

mechanisms responsible for sudden loss of consciousness is cerebral ischemia, the other two being changes in the composition of the blood and reflex cerebral dysfunction. Cerebral ischemia can be generalized or localized. The former occurs following a sudden fall in blood pressure, which in turn is due to loss of peripheral resistance, or a rapid decrease in cardiac output. Thus far only the mechanisms causing a loss of peripheral resistance have been discussed. They may be active or passive. Active reflex peripheral vasodilatation is seen in the vasodepressor forms of vasovagal, carotid sinus and hyperventilation syncopes. In addition, reflex vasodilatation may occur as a result of stimulation of certain pressoreceptors, but further study is necessary to insure that these play a role. These include reflexes from the aortic arch, from the pulmonary, coronary and cerebral vessels, and from the heart itself. Passive loss of peripheral resistance is seen in temporary and chronic orthostatic hypotension; the temporary form being due to failure of normal vasoconstriction in the upright position, or following the use of certain drugs. Chronic orthostatic hypotension is either secondary to central nervous system or idiopathic. The other mechanisms causing a fall in blood pressure and its resulting cerebral ischemia will now be considered.

Decreased Cardiac Output

Sudden decrease in the cardiac output with resulting syncope is often due to organic heart disease. Bishop [*55*] records 247 of 5,000 patients with organic heart disease who had fainting as their primary complaint. Loss of consciousness may come about as a result of (1) cardiac standstill, (2) decrease in the stroke volume, or (3) the decrease in cardiac output may be extracardiac in origin.

Cardiac Standstill. Adams-Stokes syndrome: In Adams-Stokes syndrome pre-existing partial or complete heart block is present, with ventricular rates below 40 to 50. Syncope is not due to the slow heart rate but rather to asystole, multiple premature beats or ventricular fibrillation. This occurs during the delay in transition from a normal sinus rhythm or partial block to that of an idioventricular rhythm or complete heart block [*54*]. The duration of asystole necessary to produce attacks is variable, as short as three seconds or longer than fifteen seconds [*11*], depending upon the condition of the cerebral vessels, and the position and activity of the body. Loss of consciousness sometimes occurs after exertion. In the latter instance the cardiac output is unable to increase relative to the demands of the body.

Cardioinhibitory form of carotid sinus syncope: The vasodepressor form of carotid sinus syncope has already been discussed. Of Ferris, Capps and Weiss's fifty-six cases of carotid sinus syncope, 34 per cent were of the cardioinhibitory form [*13*]. While a hypersensitive or irritable carotid sinus is not infrequently seen, syncope secondary to this is rare. Of Nathanson's 115 patients with a hyperactive, cardioinhibitory carotid sinus reflex, only six had spontaneous syncope [*56*]. Approximately half of the patients with this form of syncope have evidence of arteriosclerotic heart disease or hypertensive cardiovascular disease [*57*], and thus is evidently one of the factors causing sensitivity of the reflex arc, some of the others having already been discussed. The stimulus, however, originates in the carotid sinus, pressure over this area resulting in unconsciousness in seven to ten seconds, with little or no change in the blood pressure [*12*]. Electrocardiographic records indicate, in addition to asystole, bradycardia, varying degrees of A-V block up to complete heart block, and premature ventricular contractions.

Cardioinhibitory form of vasovagal syncope: The other reflex type of asystole causing loss of consciousness is the cardioinhibitory form of vasovagal syncope, differing from the one just discussed only in that the entire reflex arc is located within the vagus pathway. Carotid sinus pressure has no effect. Afferent stimuli arise from the esophagus, pharynx, larynx, mediastinum and bronchi. This type of syncope is apt to occur following instrumentation, as with a bronchoscope, or with swallowing in patients with esophageal diverticulas [*11*]. The area of hypersensitivity is not necessarily afferent in location but may be at the efferent end of the arc, in the heart. In patients with coronary artery disease it has been possible to induce cardiac standstill by distention of the stomach with a balloon [*58*].

Decreased Stroke Volume. This is the second important mechanism accounting for a fall in cardiac output and may occur as a complication of valvular disease, notably aortic stenosis; as a result of a weakened myocardium secondary to myocardial ischemia; and as a result of certain arrhythmias.

Valvular lesions: The best known example in which syncope occurs is aortic stenosis, being

recorded in from 12 to 32 per cent of cases [*59–61*], although 12 to 20 per cent is probably a closer figure. Most always, loss of consciousness occurs following some form of exertion and is preceded by angina and dyspnea. The exact mechanism causing loss of consciousness is not precisely known. Electrocardiograms have been taken in only a few instances during the syncopal period and have failed to reveal any consistent pattern: bradycardia, tachycardia, premature ventricular contractions and A-V dissociation all taking place [*10*]. Other possibilities exist: Friedberg [*54*] notes that syncope occurs in patients with extreme valvular narrowing and ventricular hypertrophy. In these subjects there is a markedly increased left intraventricular pressure which is sufficient to meet the body's needs under ordinary circumstances, but with exertion the heart is unable to meet the demands of the body as rapidly as necessary, with resulting loss of consciousness. The fact that angina almost always precedes the syncopal episode lends strong support to this, there being a relative coronary insufficiency. An associated weakened myocardium relative to the impaired coronary flow undoubtedly helps to reduce the cardiac output further. Not to be overlooked, too, is the peripheral vasodilatation associated with exercise, with its resulting decrease in venous return. Finally, reflexes from an engorged pulmonary vessel or heart, as previously discussed, might also play a role.

Other valvular lesions rarely cause syncope. These include aortic insufficiency and mitral stenosis. In the latter instance an additional factor is the occasional occurrence of paroxysmal tachycardia, flutter or fibrillation.

Myocardial ischemia: Loss of consciousness rarely occurs following angina pectoris or coronary insufficiency but is somewhat more frequent in myocardial infarction [*11,62*] and is apt to be severe and prolonged. There may be a reduction in stroke volume from a weakened myocardism. Arrhythmias may develop, including ventricular tachycardia, heart block, fibrillation and multiple premature beats. There may be reflexes from coronary vessels, such as the Bezold-Jarish reflex. Finally, there can be associated pain, although unconsciousness not uncommonly occurs in the complete absence of pain.

Arrhythmias: Various mechanisms may account for episodes of syncope in association with arrhythmias. In the case of multiple runs of premature beats, the weak beats are inadequate to eject a sufficient amount of blood. In the atrial and ventricular tachycardias, stroke volume progressively decreases above rates of 180 per minute due to the shortened ventricular filling phase during diastole. Thus patients with tachycardia, rates over 180, show an incidence of fainting of over 50 per cent [*63*]. Finally, the delay in transition from one rhythm to another may cause asystole for a sufficiently long period to induce unconsciousness [*64*].

Extracardiac Causes. This is the third main cause of a decrease in cardiac output. Elevation of intrathoracic pressure, such as occurs with positive pressure breathing, defecation with prolonged straining, and in some instances protracted cough, can bring about a reduction of venous return sufficiently great to cause fainting. Positive G forces also will rapidly bring about a reduction in venous return. Syncope in these instances is very transient and the cause readily discernible. Pulmonary hypertension is not uncommonly accompanied by fainting, especially after exertion; Dresdale et al. [*65*] recorded an incidence of 20 per cent of thirty-nine patients with loss of consciousness. A pain not unlike angina may be associated with effort in these subjects, in whom syncope evidently is the result of inability of the heart to increase the cardiac output relative to the needs of the body. The arterial PO_2 has been found to be normal during the period of unconsciousness in primary pulmonary hypertension [*66*].

To recapitulate briefly: Decreased cardiac output is the other main mechanism whereby generalized cerebral ischemia is brought about. A reduction of cardiac output occurs as a result of asystole, an impaired stroke volume, or a decrease in venous return from extracardiac causes. Syncope as a result of asystole occurs chiefly in Adams-Stokes attacks but may be seen also in the cardioinhibitory forms of carotid sinus and vasovagal syncopes. Reduction in stroke volume occurs with extensive valvular disease, myocardial ischemia, and following certain arrhythmias. Extracardiac conditions causing a decrease in venous return include chiefly prolonged cough, straining with defecation, positive G forces and pulmonary hypertension.

Localized Cerebral Ischemia

In most instances localized cerebral ischemia is secondary to vascular disease, loss of consciousness occurring as a result of advanced

cerebral arteriosclerosis or thrombosis, or carotid artery thrombosis. Focal neurological signs usually accompany such cerebral ischemia, and unconsciousness, when it occurs, is often without warning and prolonged. So-called small or little strokes are not unlike syncopal episodes.

There is a group of syncopes which has been attributed to localized cerebral vasospasm. Weiss et al. [*11–13*] first demonstrated a central type of carotid sinus syncope in which carotid sinus stimulation caused unconsciousness in three to four seconds without change in blood pressure or heart rate, and which he thought was due to a reflex acting upon a mid-brain center regulating consciousness. Whether or not a central form of a carotid sinus syncope truly exists has been seriously questioned, and in many such instances unconsciousness can be explained by partial or complete occlusion of the contralateral carotid artery [*67a,67b*]. Thus compression of the carotid sinus on the unaffected side causes immediate cerebral ischemia and syncope. Toole [*67c*] has recently described a series of patients with loss of consciousness following carotid artery compression as well as carotid sinus compression. All had simultaneous loss of temporal artery pulsations. In two patients in whom syncope occurred only following carotid sinus pressure, infiltration of procaine into the sinus adventitia and ipsilateral cervical sympathetic block failed to alter the response. It was postulated that carotid sinus pressure blocked collateral circulation from the external carotid artery. Such a situation would be exceedingly rare. Despite such evidence, focal and generalized electroencephalographic abnormalities have been shown to occur upon compression of the carotid sinus, but not by occlusion of the carotid artery, and can well be explained by spasm of the cerebral vessels [*10*]. There is other evidence for a reflex mechanism inhibiting a conscious center in the cortex [*68,69*]. Furthermore, it has been demonstrated that direct stimulation of certain areas of the hypothalamus in man can cause fainting [*70*].

Localized vasospasm has been incriminated as responsible for the syncopal episodes rarely seen in migraine, hypertensive encephalopathy and neurocirculatory collapse, the latter being a specialized form of decompression sickness seen (rarely) at high altitudes and associated with focal neurological signs. Finally, localized cerebral ischemia has been suggested as responsible for cough syncope. McIntosh et al. [*71*] have postulated that the increase in cerebrospinal fluid pressure transmitted from an elevated intrathoracic pressure causes extravascular compression of cerebral vessels and "squeezes" blood from the cranium. While an attractive thought, this does not explain the failure of patients to develop loss of consciousness when they execute the Valsalva maneuver.

Syncope Caused by Changes in the Chemical Composition of the Blood

It is possible to have a normal or even increased blood flow to the brain but lose consciousness because of the lack of some essential substance necessary for cerebral metabolism. Thus hypoxia, hypocapnia, hypercapnia, hypoglycemia and nutritional disturbances all can cause syncope or syncopal-like episodes. Of course, many agents can cause unconsciousness such as alcohol, carbon monoxide, barbiturates, insulin (exogenous) and methemoglobin. But these cause coma, discussion of which is beyond the scope of this paper.

Hypoxia. Arterial unsaturation is the primary reason for the occurrence of unconsciousness at high altitudes. Thus at 30,000 feet, breathing ambient air, consciousness can be sustained for several minutes, while above 40,000 feet a person will become unconscious in twelve to fifteen seconds. Clinically, arterial unsaturation is an uncommon cause of syncope but does cause coma. In patients with congenital heart disease, however, syncope is not infrequently seen following exertion. In this instance loss of consciousness apparently is due to the combination of a greater percentage of unsaturated blood returning from the periphery, and an increase in the right to left shuntings of blood. Syncope is also known to occur in patients with congenital methemoglobinemia [*82*].

Hypocapnia and Hypercapnia. Hypocapnia occurs with hyperventilation. It is doubtful whether the low arterial P_{CO_2} *per se* causes unconsciousness, since in properly trained subjects the value may go as low as 10 mm. Hg without loss of consciousness [*72*]. It is, however, a contributory factor. Hypercapnia may, through respiratory depression, cause syncope in asphyxia.

Hypoglycemia. Hypoglycemia as a cause of syncope occurs in association with islet cell tumors, and may be a contributory factor in Addison's and Simmonds' disease. The onset of unconsciousness is usually gradual but may be rapid if preceded by exertion. A word should

be said about functional hypoglycemia. This rarely causes loss of consciousness [*73*]. It causes syncope-like symptoms such as sweating, anxiety, dizziness, faintness and palpitation; and it may be a contributory factor in other forms of syncope, especially the vasovagal type and in hyperventilation. The level the blood sugar must drop to varies with different subjects, but in general must fall below twenty to thirty mg. per cent. Exogenously administered insulin as a cause of temporary loss of consciousness is too well known to discuss.

Nutritional Deficiencies. Discussion of the various food and vitamin deficiencies which may cause loss of consciousness is not within the realm of this paper. It should be mentioned, however, that fainting is commonly seen in victims of famine, particularly after prolonged standing, and may be used as an index of the degree of starvation [*74*].

Cerebral Dysfunction

Loss of consciousness may occur as a result of (for lack of a better term) cerebral dysfunction. The main group under this heading is of course epilepsy, both idiopathic and symptomatic. While, strictly speaking, epilepsy should not be considered a form of syncope, it is often associated with loss of consciousness. Indeed, it may be impossible to separate the two. To compound the difficulties, persons with epilepsy may have ordinary syncope while patients who faint can have convulsions. The experiments of Rosen and his associates [*75*] are interesting in this regard. These investigators induced rapid cessation of blood flow to the brain by means of an occlusive cuff around the neck which was inflated suddenly. Fixation of the eyes, blurring of vision, constriction of visual fields, paresthesias of the extremities and tonic or clonic convulsions occurred in most subjects. Loss of consciousness took place in an average of five to six seconds. Involuntary micturition and defecation occurred in many of the subjects. In other words, a severe episode of syncope can duplicate an epileptic episode in every way.

It has already been pointed out that there is some evidence to suggest the existence of a center which influences the conscious state. It would seem that this center is influenced not only by vascular changes but reflex changes as well, and it is perhaps these reflexes which induce unconsciousness in cerebral dysfunction, whether it be due to epilepsy, concussion or the central type of carotid sinus syncope. Little is to be gained by further speculation until more evidence is available regarding the mechanisms of these various forms of unconsciousness.

To summarize briefly: Cerebral ischemia, changes in composition of the blood and cerebral dysfunction are the three basic abnormalities responsible for syncope. The various causes under each of the three groups have been discussed and, when known, the mechanisms of loss of consciousness have been considered. Since the mechanisms responsible for unconsciousness are different in each case, the clinical characteristics differ. What these clinical features are will be apparent from the following study.

CLINICAL FEATURES

From the record files of the Cleveland Clinic between the years 1945 and 1957, charts indicating the diagnosis of syncope were reviewed in detail. The cases had to satisfy two basic prerequisites. First, there had to be complete loss of consciousness; second, an adequate history, physical examination and laboratory studies must have been recorded. In all, probably close to 1,000 charts were reviewed and over 500 were selected as satisfactory for analysis.

It is to be emphasized at the outset that this study in no way seeks to obtain precise statistical information as to the incidence of the various types of syncope, the frequency of occurrence of other associated diseases, or the incidence of the various associated characteristics. In other words, qualitative information only could be obtained, for a number of reasons inherent in the study. And it is readily apparent that under the best circumstances a specific diagnosis is not always possible.

Despite these difficulties, however, many useful facts were obtained. The syncopal episode itself warranted some study of course; however, events leading to and to a lesser extent following the bout of unconsciousness were considered to be of greater import, since in most instances the period of syncope itself was disappointingly uncharacteristic. Of less importance than what the patient felt was what the patient was doing immediately prior to the period of unconsciousness, how long it took before syncope occurred, and for how long he or she was unconscious. Relatively little information can be derived from how or what the patient feels, since the body's reaction to all forms of syncope is essentially the

TABLE 1
BREAKDOWN OF VARIOUS CAUSES OF SYNCOPE SEEN IN 510 PATIENTS

Cause	No.
Vasovagal	298
Orthostatic hypotension	28
Epilepsy	26
Cerebral vascular disease	24
Unknown etiology	23
Postmicturition	17
Adams-Stokes syndrome	17
Hyperventilation	15
Hypersensitive carotid sinus	15
Tussive	13
Aortic stenosis	9
Paroxysmal tachycardia	8
Angina pectoris	4
Hysteria	4
Myocardial infarction	3
Pulmonary hypertension	2
Migraine	2
Hypertensive encephalopathy	2
Total	510

same, differing only in the degree of severity of the syncopal episode.

Table 1 classifies the various syncopes encountered in the total of 510 case reports studied. Each was reviewed in terms of age, sex, associated disease, precipitating factors, activity of the patient immediately prior to the onset of syncope, the warning symptoms and their duration, physical changes associated with the unconscious episode, duration of the period of unconsciousness and the postsyncopal reactions. It was not possible of course to obtain all this information from each chart, but enough charts were studied to give a composite picture. The various types of syncope will now be discussed.

Syncope Secondary to Reflex Loss of Peripheral Resistance. Vasovagal syncope: This was by far the most common form of syncope encountered, being found in 298 patients—more than all other forms combined. Contrary to the views of some, this form of syncope was not found just in young adults; it was as prevalent above the age of forty as below. It occurred somewhat more frequently in males, although not significantly so. In 117 of these patients there was no associated disease; of the remainder, a large number had anxiety tension states. Common too were functional gastrointestinal problems including indigestion, irritable colon and duodenal ulcer. Various incidental, non-related diseases were present in the rest, such as organic heart disease, hypertension, arteriosclerosis, chronic pulmonary disease and gallbladder or kidney disease.

Precipitating factors often included a history of emotional tension, fear, apprehension, fatigue, lack of food or sleep, mild trauma with associated pain, a hot and/or close environment, the sight or withdrawal of blood, excess intake of alcohol, indigestion or other forms of abdominal discomfort, neuromuscular chest pain, instrumentation of any sort, and witnessing other people faint. The list is by no means complete. Actually, any stimulus capable of creating enough stress was sufficient to induce a vasovagal episode. In many instances, however, there seemed to be no precipitating circumstance; many said they were "easy fainters," and most had fainted a few times in the past, but this was not invariably true. The converse of this, that is, the absence of preceding faints, in no way ruled out vasovagal syncope.

In the presyncopal period the patient in most instances was standing immediately prior to loss of consciousness, but the development of symptoms in the sitting position was not uncommon. No instance occurred in which symptoms *began* in the recumbent position. Warning phenomena included marked weakness, sweating, epigastric discomfort, dizziness, lightheadedness or, in a few instances, vertigo, blurred vision, nausea, occasional vomiting, sighing respiration, tinnitus, a feeling of generalized numbness or warmth, paresthesias in the extremities, palpitation, headache, excess salivation and pallor. The duration of these warning phenomena varied—in mild cases as long as a few minutes. In severe cases with sudden onset the patient was apt to have as little warning as ten to twenty seconds. Some patients stated that they had no warning at all; this is doubtful, however, for in all probability there was some amnesia for the presyncopal period. Also, not infrequently patients cannot recall specific sensations but when prompted with direct questions do remember them. Many patients had learned to recognize the prodromata and were able to ward off unconsciousness by lying down. This was not true for certain other forms of syncope.

The characteristics of the syncopal episodes depended upon the rate of onset and severity of the attack. During the period of unconsciousness the patient was reported to be pale or ashen in color, the skin cold and covered with perspira-

tion, the pulse feeble or unobtainable and slow, and the pupils dilated. In a number of instances urinary incontinence occurred and, rarely, fecal incontinence. Tonic or clonic movements were uncommon but not rare. There were no instances of reported tongue biting, occurrence of syncope during sleep, or gustatory or olfactory aura. Histories varied in the number of symptoms recorded, not only for the syncopal period but for the periods before and after as well; some having a great many listed, some few or none, depending on the severity and duration of the episode and the acuity of the examiner.

The duration of the unconscious episode varied from several seconds to a few minutes in most instances. A number were reported to be unconscious ten, twenty and even thirty minutes. Rarely, some were reported to be "out" from one to two hours; in such instances, however, it was more than likely that some other form of syncope was responsible, for example, trauma to the head sustained during the fall might have been a contributing although unrecorded factor.

In the postsyncopal period most patients awoke after a few moments mentally clear and without residue; however, mild and transient discomfort not infrequently occurred. Thus the patient was apt to be nervous, weak, dizzy, nauseated, mildly but *briefly* confused or have a headache. Some felt nervous and upset or weak for one or two days. The degree of residua seemed to be related to the duration of the attack, often being minimal or absent when the attack was brief. Residua that lasted for more than a few minutes were more likely to be a reflection of the underlying nervous tension.

The diagnosis of vasovagal syncope would seem to be based especially on a history of tension and/or specific stressful factor. The occurrence in a young patient did not in particular favor vasovagal syncope, but did help rule out some of the other forms which characteristically appear in the older age groups. The presyncopal period was not characteristic except for the absence of initiation in the recumbent form. Thus the period of syncope was notable more for what was absent than for what was present; and of course, of greatest importance, no other abnormality could be found which might be responsible for another form of syncope.

Hyperventilation syncope: While the hyperventilation syndrome is very common, syncope secondary to hyperventilation was rare and found in only fifteen patients. Patients were usually in their twenties or thirties and most often female; indeed, this was the only form of syncope found more often in females. Associated findings included such functional disturbances as tension states, tension headaches, irritable colon and functional indigestion. Precipitating factors were limited to nervous tension and almost always could be elicited. The presyncopal period was distinguished by sensations of lightheadedness, a faraway or floating feeling, dizziness, palpitation, weakness, trembling, hyperhydrosis, flushed warm face, numbness and tingling in the hands or feet or perioral region, dry mouth, blurred vision, neuromuscular chest pain, generalized hot or cold sensations, marked apprehension, unsteadiness, inability to think clearly, muscular twitchings and, most often, shortness of breath and/or sighing respirations. Tetany, whether in the presyncopal period or during the attack of unconsciousness, was rare, in contrast to common supposition. Unlike other forms of syncope, the duration of the warning symptoms was relatively prolonged, often lasting over a period of a few minutes; however, it is known that hyperventilation syncope may occur in as short a time as twenty to thirty seconds. The patient was usually standing or sitting but not lying down.

The syncopal episode was not especially different from that of vasovagal syncope unless tetany happened to be present. The patient should be questioned quite carefully as to whether he or she were truly unconscious. Many had a "far away feeling" and were unable to talk but could hear voices in the distance. Not infrequently there would be recorded the fact that the patient was "out" for hours. Actually, these patients are not really unconscious for longer than a few minutes but continue to hyperventilate for a prolonged period, retaining many of their symptoms.

The postsyncopal period was notable particularly in that many patients felt marked weakness, apprehension and sweating; in short, many of the presyncopal hyperventilation symptoms. Unlike vasovagal syncope, the patients usually did not feel well and mentally clear within a few moments after recovery, but tended to retain their residue for long periods of time, sometimes hours.

Hyperventilation syncope is most apt to be confused with paroxysmal tachycardia, hypoglycemia and hysteria. Paroxysmal tachycardia

can be distinguished by the sudden onset and cessation of the arrhythmia, and by the fact it precedes the other symptoms; in fact it is the first symptom. Hypoglycemia may closely simulate hyperventilation syncope and may summate with it; but in functional hypoglycemia at least, consciousness is not lost, while the organic form can be duplicated by fasting the patient. Hysterical "syncope" is not really syncope and will be discussed more fully later.

In short, then, hyperventilation syncope can be distinguished by its occurrence in young women under nervous tension, the associated symptoms of hyperventilation, in particular, numbness and tingling of the extremities or perioral region, sighing respiration or shortness of breath, and the prolonged residua. Tetany, if it occurs, is practically diagnostic provided the patient was truly unconscious, but is seldom seen. Most often the episode can be duplicated by voluntary hyperventilation but not invariably so.

Tussive syncope: This occurred in thirteen patients, almost all males between the ages of forty and sixty years. Associated conditions were primarily chronic lung disease such as asthma, emphysema or chronic bronchitis. This was one of the simplest forms of syncope to diagnose, a history invariably being obtained of the patient coughing *immediately* prior to the attack of unconsciousness. It did not necessarily have to be a prolonged paroxysm of coughing. There were no other outstanding precipitating factors. Patients were standing or sitting at the time of unconsciousness; in the former instance their head was apt to slump forward without their falling out of the chair. Usually no warning symptoms at all were experienced, except perhaps for transient lightheadedness or dizziness. Two patients were laughing heartily immediately before losing consciousness rather than coughing. During the period of unconsciousness a few of the patients were reported to be pale and sweaty or to have mild clonic convulsions. Almost always the patients reported that they were unconscious for not more than a few seconds, at most, a half to one minute. The postsyncopal period was notable by the absence of residua, the patients feeling mentally clear and simply carrying on with what they were doing. It was not always possible to duplicate a syncopal episode by having the patient cough or exert a Valsalva maneuver, although in some instances a marked hypotension would develop. Derbes and Kerr [*76*] have written an excellent monograph on cough syncope, describing the clinical characteristics in detail.

Thus cough syncope was distinguishable by being preceded by coughing (or laughing in some instances), by brief warning and duration, the absence of postsyncopal residua and, usually, the history of many such episodes in the past.

Syncope Secondary to Passive Loss of Peripheral Resistance. Orthostatic hypotension: This form of syncope was seen in twenty-eight patients. Most were in their fifties and sixties, although not infrequently orthostatic hypotension was the cause of the unconscious episode in younger age groups, including those in their teens. Males were mostly affected. About 25 per cent of these patients had evidence of generalized arteriosclerosis and almost 30 per cent had diabetes mellitus, usually with diabetic neuropathy and retinopathy. Other associated diseases were not particularly characteristic. The precipitating factor in every case was either a sudden change in position—especially in the older age groups—or prolonged standing, the latter being somewhat more apt to occur in a hot environment when the patient was required to stand motionless. Some of the other precipitating factors have already been discussed in the first portion of this paper; however, in almost half of the patients no apparent precipitating factor was discernible from the records. Symptoms would begin as soon as the upright position was attained or within a few minutes thereafter. In some instances it followed prolonged standing after exercise. Warning symptoms included dizziness, lightheadedness, weakness and epigastric discomfort, followed by collapse. A few patients had no warning at all. Other signs of intense autonomic stimulation, such as seen in vasovagal syncope, were not noted. Warning phenomena did not last more than several seconds and usually less than thirty seconds. A few patients had mild convulsions or incontinence during the syncopal episode but otherwise the period of unconsciousness was not especially characteristic and lasted from a few seconds to a few minutes. Postsyncopal residua were absent.

Thus orthostatic hypotension is distinguished by the development of unconsciousness following sudden changes in position, is usually seen in patients with diabetes mellitus or generalized arteriosclerosis, and can be established by the demonstration of a low blood pressure, either relative or absolute, in the upright position.

Postmicturition syncope: Postmicturition syncope

was an unusual form of unconsciousness, occurring in seventeen patients all but one of whom were males. It was characteristically seen in patients in their twenties and thirties but occasionally occurred in older subjects. Other associated disease was absent or, if present, was noncontributory. The usual story was that of a patient arising in the middle of the night, going to the bathroom to void, and losing consciousness either immediately after micturition or on the way back to bed. Some had premonitory sensations of weakness, dizziness, nausea, lightheadedness or a limp feeling, while some had no warning at all. The duration of these symptoms was not more than several seconds and the period of unconsciousness lasted only one to two minutes. No unusual signs were recorded during the syncopal episode. In a few patients the history revealed loss of consciousness in the early evening but in these instances they had been watching television in the recumbent position for several hours; then, during a commercial, they had run upstairs to void and lost consciousness. This group should really be considered as having a special form of orthostatic hypotension which differs in not occurring in people with diabetes mellitus or generalized arteriosclerosis, although presumably it can readily occur in such persons. A few of these patients had had episodes of vasovagal syncope in the past. The history is obviously diagnostic.

Syncope Secondary to a Decrease in Cardiac Output. Adams-Stokes syndrome: This form of syncope was seen in seventeen patients, most of whom were in the fifty to sixty year old age group. Unlike most other forms of syncope there was no particular sex distribution. While many of these patients had clinical evidence of complete heart block at the time of their initial physical examination, with rates usually below the mid-forties, some had normal rhythms when first seen. However, the electrocardiogram usually demonstrated varying degrees of A-V block or bundle branch block (usually right bundle branch block). Somewhat similar to the data obtained in tussive syncope was the history of frequent multiple attacks occurring in any position. Episodes took place in one patient following exertion and in one during sleep. Sensations preceding the unconscious episode included dizziness, a faint feeling, lightheadedness, an odd sensation in the stomach, slowing of the pulse or thumping of the heart. Most of these patients had a warning of several seconds but some apparently had no premonitory feelings at all. The duration of unconsciousness varied from ten to fifteen seconds to a few minutes. The only distinguishing feature of the unconscious episode was occasional convulsions or fecal incontinence. Postsyncopal residua were not identifying except perhaps when convulsions occurred, in which case recovery took a little longer. No records were available on the cardiac rhythm during the episode. While a diagnosis of Adams-Stokes attacks is not hard to make in some patients, the history of repeated attacks, some in the recumbent position, and the clinical evidence of complete heart block may all be absent, and unless an attack is witnessed the diagnosis may be very difficult to make.

Carotid sinus syncope—cardioinhibitory form: While a hypersensitive or irritable carotid sinus reflex is a not uncommon finding, syncope secondary to this reflex was rare in this series of patients and found in only fifteen cases. Most were males over sixty years of age, with organic heart disease and hypertension as the most frequent associated conditions. A few patients had symptoms of irritable colon. Other associated disease included chronic pulmonary disease, generalized arteriosclerosis and hiatus hernia. Precipitating factors usually were not apparent. The patients were not for the most part engaged in any unusual activity prior to the onset of unconsciousness, although in a few cases sudden turning of the head or the wearing of a tight collar could be elicited. Most patients were standing or sitting at the time of unconsciousness. Warning symptoms, when present, did not differ significantly from those noted in the Adams-Stokes attacks, and in some instances there were no prodromata experienced. The characteristics of the unconscious episode and the postsyncopal period also were not very different from those of Adams-Stokes attacks. The main difference between the two could be demonstrated during the physical examination. A normal sinus rhythm would be evident and pressure over the carotid sinus (not over the carotid artery) would precipitate an attack exactly like that previously experienced by the patient. It is important to emphasize that mere bradycardia, dizziness, a faint feeling, or even asystole for one to two seconds is not sufficient to make the diagnosis. Carotid sinus pressure must result in unconsciousness. (The former response merely indicates an irritable carotid sinus reflex.) In rare instances, carotid sinus syncope is a transient

phenomenon, i.e., it may occur during the convalescent phase of myocardial infarction but not otherwise. Unconsciousness following both carotid sinus and carotid artery pressure suggests contralateral carotid thrombosis rather than a hypersensitive carotid sinus reflex.

Aortic stenosis: Syncope as a result of aortic stenosis was noted in nine patients, usually in the forty to sixty year old age group. Most had rheumatic heart disease, a few had calcific aortic stenosis. The loss of consciousness was preceded in almost every case by exertion, either minimal or moderate in amount, and for a few or several minutes. Immediately before the unconscious episode there were premonitory symptoms of dizziness, lightheadedness, weakness, sweating, palpitation, a feeling of faintness, shortness of breath and often angina. In some cases syncope occurred without any warning sensations. Often the premonitory phenomena were delayed sufficiently long to allow the patient to abort an attack by lying down, although sometimes unconsciousness would occur even then. The syncopal episode was noteworthy for the somewhat longer duration of the unconscious period, such as five, ten, twenty, even thirty minutes. Postsyncopal residua seemed to be a little more severe than with other forms of syncope, with marked weakness, occasional shortness of breath, angina and one instance of nausea and vomiting. The diagnosis is easily made in view of the history of attacks following exertion, the loss of consciousness preceded by shortness of breath and angina, and the demonstration of aortic stenosis.

Angina pectoris and myocardial infarction: Seven patients were seen with loss of consciousness following myocardial ischemia, four after myocardial infarction and three following angina pectoris. Most of these patients were males over fifty. In all probability there were many more patients with unconsciousness after myocardial infarction in this thirteen-year period, but the diagnosis in the charts was listed under the primary disease and unconsciousness was not considered a major diagnosis. Cookson [77] has reported on 200 cases of acute infarction; there were ten patients who lost consciousness at the onset and five more subsequently. In the cases of syncope with angina, attacks were precipitated with exertion or excitement. Unconsciousness occurred without warning or with such prodromata as dizziness, blurred vision, numbness and tingling in the left arm and hand, weakness, sweating, nausea, and, of course, chest pain—the number of symptoms and their duration depending upon the degree of myocardial insufficiency. In a few instances a rapid irregular heart action immediately followed the onset of the angina. Unconsciousness, whether after angina or myocardial infarction, did not seem to be dependent on the amount of chest pain; and with myocardial infarction occasionally occurred in the complete absence of chest pain, even after consciousness returned. As with syncope in angina secondary to aortic stenosis, loss of consciousness could occasionally be aborted by lying down. The duration of the warning symptoms was usually less than thirty seconds. One patient had warning symptoms initially lasting twenty seconds, with unconsciousness for two to three minutes. As his disease progressed his warning period decreased to about ten seconds and his unconscious spells increased to a half to several hours.

In the more severe cases the syncopal episode was characterized by prolonged loss of consciousness, as just mentioned, sometimes for hours but usually closer to a half hour. Some patients had both urinary and fecal incontinence. Surprisingly, no convulsions were recorded. Following the return of consciousness in some cases there was chest pain, marked weakness, confusion, nausea or headaches. None of the cases of syncope were seen during the acute phase of myocardial infarction, the diagnosis being a presumptive one made from the history of characteristic syncope, no known previous infarction and electrocardiographic evidence of a recent or remote occlusion.

While loss of consciousness following angina is not particularly difficult to diagnose when there is a characteristic history, the possibility of a myocardial infarction being responsible may not be thought of, especially when no history of chest pain can be elicited. It should be considered, however, in every patient in the proper age group with a prolonged period of unconsciousness, and serial electrocardiograms should be obtained.

Paroxysmal tachycardia: Eight patients fall in this group, mostly males over fifty. Associated arteriosclerotic heart disease, valvular heart disease or generalized arteriosclerosis were noted in a few patients, but organic heart disease did not necessarily have to be present. Warning phenomena included the sudden onset of a rapid, irregular heart beat, sweating, dizziness,

weakness, faintness, and nausea or vomiting. Duration of the warning sensations depended upon the cardiac rate and activity of the patient, and presumably would depend also on when the rhythm would change from normal to abnormal. In some cases premonitory symptoms did not last more than several seconds. The duration of unconsciousness sometimes was short (a few minutes), sometimes longer, presumably depending upon the mechanism of the loss of consciousness. Neither the unconscious spell nor the recovery period had any distinguishing features. The diagnosis is relatively easy to make if the patient has a *sudden* onset of an arrhythmia *followed* by sensations of impending syncope.

Syncope Secondary to Localized Cerebral Ischemia. Cerebral vascular disease: This was a relatively common form of syncope, occurring as a presenting complaint in twenty-four patients. Most of these were in the older age groups with clinical evidence of generalized or cerebral arteriosclerosis. Warning symptoms, when present, were not infrequently characterized by focal neurological changes such as ataxia, confusion, inability to talk or see, incoherent speech, hemiparesis, numbness of an extremity and facial asymmetry. A few had uncharacteristic warning signs such as dizziness or weakness, and often there were no warning symptoms at all. In the former instances the premonitory signs lasted only several seconds. None of the patients were seen during the unconscious episode but presumably would show focal neurological signs in some instances. No convulsions were recorded, a few had urinary or fecal incontinence. Unconsciousness was apt to be prolonged, with recovery distinguished by confusion, disorientation, amnesia, weakness or neurological residua. A characteristic history in an elderly patient usually leads to an easy diagnosis. It should be pointed out, however, that several of these patients had no characteristic warning or residua, but the duration of unconsciousness was prolonged and there was clinical evidence of cerebral arteriosclerosis, thus allowing a presumptive diagnosis.

Cerebral Dysfunction. Epilepsy: Epilepsy with fainting as the presenting complaint was present in twenty-six patients. There was no characteristic distribution as to age or sex since presumably these patients represented symptomatic as well as idiopathic epilepsy. Epilepsy was one of the most difficult of all things to rule out clinically. In many instances the presyncopal, syncopal and postsyncopal periods were remarkably similar to vasovagal syncope. In fact, it is well known that many of the factors which precipitate ordinary vasovagal syncope will also precipitate epileptic seizures, i.e., hypoglycemia, fatigue, lack of sleep and tension. To confuse the problem further, some subjects with epilepsy have a normal electroencephalogram and a few will revert to normal after previously being reported as abnormal. One or more of the following was considered evidence in favor of an epileptic attack: occurrence during sleep or in the horizontal position, prolonged aura (especially olfactory or gustatory), biting of the tongue, fecal incontinence, stertorous respiration, prolonged loss of consciousness or occurrence in the erect position, flushed face, and, of course, a grand mal convulsion. It should be emphasized that almost all these phenomena can occur in other forms of syncope, but they are very uncommon. An abnormal electroencephalogram, of course, supports the diagnosis but it should be pointed out that the electroencephalogram may be normal in as many as half of epileptic patients [*78*]. In the recovery period, prolonged confusion and muscle soreness are apt to be present.

Hysterical "fainting": This was rare in the present series occurring in only four patients, all females. Strictly speaking, hysterical "fainting" should not be considered a form of syncope since the patients actually do not lose consciousness, i.e., close questioning may reveal that the patient could understand what was going on, but could not talk or arise. Bizarre movements or sounds may occur during the "unconscious" episode, or consciousness may be gained and lost intermittently. Few of the characteristic symptoms of other forms of syncope can be consistently elicited. Warning signs are absent, the faint occurs abruptly in the presence of others, the patient never injures herself (most of these occur in young women), the "unconscious" episode is very dramatic and, significantly, the patient seems entirely unconcerned about her condition. There is no pallor, change in pulse or blood pressure, and no sweating. Hyperventilation is often present and associated symptoms of hyperventilation may confuse the picture. The patient may be "out" for hours yet recover promptly without residua. The episode may occur in any position and there is no prompt recovery in the recumbent position [*79*]. Diagnosis should not be difficult if care is taken in obtain-

ing the history and performing the physical examination. One of the patients in this series was thought to have carotid sinus syncope as pressure over the sinus presumably caused unconsciousness; however, pressure over the lower part of the neck also resulted in "unconsciousness."

Unknown causes of syncope: On occasion it is not possible to identify the kind of syncope one is dealing with; in this particular series there were twenty-three such cases. Most of these patients were in their fifties or sixties. Warning symptoms were often absent or, if present, were not helpful. The period of unconsciousness was usually prolonged but in some instances lasted for only a few minutes. Several patients had organic heart disease, hypertension or cerebral arteriosclerosis; but over half had no other diagnosis listed. In general, the syncopal attack was preceded by too brief a warning period or the period of unconsciousness was too prolonged to be a vasovagal or hyperventilation episode. There was no history of occurrence following chest pain, exertion, sudden changes in position or coughing. The attacks were not characteristic of either Adams-Stokes syndrome or paroxysmal tachycardia. On physical examination no evidence of a sensitive carotid sinus was found, nor was there postural hypotension, aortic stenosis or cardiac arrhythmias. Some of these patients were extensively investigated, having an electroencephalogram, electrocardiogram, glucose tolerance test, roentgenograms of the skull and pneumoencephalograms or arteriograms but no abnormality was found. Undoubtedly, most of these patients had subsequent attacks which could be identified but such information was not available on the charts.

A word should be said about syncope with bundle branch block; there were fourteen patients in whom an incidental finding was bundle branch block—eleven right, three left. Six of the patients had Adams-Stokes attacks, two had vasovagal syncope, two were in the unknown group just discussed. The other reported episodes were attributed to cerebral arteriosclerosis, epilepsy, aortic stenosis and postmicturition —some of these were only presumptive diagnoses. While most of these patients were over fifty years of age, a few were in their teens or thirties. The impression was gained that bundle branch block was reported somewhat more frequently than one would expect, and that in some of these patients the block had something to do with the mechanism of the attack. More precise information on this point is needed.

Miscellaneous forms of syncope included a few patients with pulmonary hypertension, migraine headaches and hypertensive encephalopathy, these diseases presumably being responsible for the syncopal attacks.

COMMENTS

Many of the difficulties encountered in the classification of syncopal attacks can be resolved by separating the syncopal episode into distinct presyncopal, syncopal and postsyncopal periods. In the presyncopal phase, of primary importance is the duration of the warning period, the position of the body, the activity the patient was performing no matter how insignificant, and the subjective sensations and associated signs, and any other symptoms the patient happened to be experiencing at the time. What some of these subjective sensations are may be of little importance but they do give a hint as to the duration of this phase—obviously the more the patient can recall, the longer the warning phase. Most of the causes of syncope can be determined from the presyncopal period alone.

During the period of unconsciousness, the most important single detail is its duration. Short attacks of a few minutes or less are usually benign provided no abnormality is found on physical examination, while prolonged episodes usually indicate serious organic disease. In the latter instance the results of a physical examination and laboratory studies are likely to be negative. Whether or not there was injury to the head should be inquired into as this might prolong the unconscious episode. Convulsions and incontinence are not always helpful; they can occur with any severe fainting spell.

In the postsyncopal period it is important to determine what residua are present and the length of their duration. Thus amnesia, muscle soreness or prolonged confusion would favor a convulsive episode, chest pain would make one suspect myocardial ischemia, focal neurological changes a stroke, and the like.

A careful history and physical examination is essential and may readily bring to light organic disease which is known to make a person susceptible to temporary loss of consciousness. It is important to include a detailed neurological examination, test for carotid sinus sensitivity, and check the blood pressure in the sitting and

standing positions. Special functional tests may be indicated such as voluntary hyperventilation, a Valsalva maneuver or even fasting for two or three days. Blood counts, urinalysis, blood sugar, a chest roentgenogram, electrocardiogram and electroencephalogram are essential, and some patients may require lumbar puncture, glucose tolerance test, skull roentgenograms or determination of urinary steroids.

It is important to realize how infrequently a single physiologic or pathologic abnormality is responsible of itself for an episode of unconsciousness. Thus in vasovagal syncope there is apt to be apprehension in addition to pain, the blood donor who faints will do so more frequently when fatigued, prolonged standing is more endangering in hot weather, the alcoholic who has not eaten is more vulnerable, the patient with cough syncope is more vulnerable during an acute exacerbation of his chronic lung disease, the irritable carotid sinus is more likely to become overt with organic heart disease, orthostatic hypotension is more pronounced during convalescence from an acute illness or with diabetic neuropathy, the patient with aortic stenosis loses consciousness after exertion, and so on. Even in normal persons a single stress is likely to have no effect but combination stresses often result in precipitous loss of consciousness. Rushmer [*80*] reports that a number of subjects during an asymptomatic arterial puncture promptly fainted after a Valsalva maneuver. Howard et al. [*81*] comment on the "mess trick" and "fainting lark"; the former being hyperventilation for one minute followed by compression of the chest, the latter consisting of hyperventilation in the squatting position, the subject rising quickly and performing a Valsalva maneuver. Both result in rapid loss of consciousness. There are many such combination stresses which will cause fainting. It should be pointed out, too, that some kinds of syncope can probably cause unconsciousness in two or more ways. This will be apparent by referring again to Figure 1.

It is not to be implied that there is always associated disease; or if disease is present, it is responsible for the syncopal episode. Vasovagal syncope, for example, is not at all uncommon in patients with incidental cardiovascular disease. Nevertheless, in many instances loss of consciousness is a reflection of some underlying abnormality and should be considered as much a symptom as the associated autonomic reactions that usually accompany it. Search should be diligently carried out for the responsible disease.

SUMMARY

Syncope is defined as a temporary loss of consciousness and is characterized by certain precipitating factors, warning signs, specific manifestations during the unconscious episode and postsyncopal residua.

The basic physiological mechanisms responsible for sudden loss of consciousness include the following: (1) Generalized cerebral ischemia due to a fall in blood pressure, and secondary to either lowering of peripheral resistance or decrease in the cardiac output. Cerebral ischemia also may be localized in nature. (2) Change in the chemical composition of blood. (3) Reflex cerebral dysfunction.

The mechanisms responsible for each of the various kinds of syncope are discussed under these headings, together with the known physiological changes occurring during syncope, and the possible contributing role played by some of the more recently described reflexes from the heart, cerebral, coronary and pulmonary vessels.

The charts of 510 patients seen at the Cleveland Clinic with syncope as a major presenting complaint have been reviewed. Eighteen different kinds of syncope were identified, and the clinical characteristics of fifteen discussed in detail.

It is suggested that the problem of determining the etiology be approached by considering the syncopal episode as having three distinct phases —presyncopal, syncopal and postsyncopal. Of importance is the duration of the warning period, the position of the body, the activity the patient was engaged in at the time of the attack, the associated symptoms and signs immediately prior to the syncopal attack, and the duration of the unconscious and recovery phases. While the reaction of the patient during the period of syncope is of some importance, i.e., convulsion or incontinence, this is of less importance since the body's response to most forms of severe, sudden loss of consciousness is essentially the same.

It is uncommon for syncope to be the result of a single factor. Multiple stresses combine to precipitate sudden loss of consciousness, especially in the presence of disease. Thus syncope should be considered a symptom of some underlying abnormality and investigation as to the cause should be made.

Acknowledgment: I wish to express my sincere thanks to Doctor Victor G. DeWolfe of the Cleveland Clinic for his review of the manuscript, and his help in its preparation; to the Cleveland Clinic Foundation for their generosity in making this material available; for the typing of the manuscript; and to Dr. Charles L. Leedham for his encouragement in starting this study.

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Colchicine*

Clinical Pharmacology in Acute Gouty Arthritis

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EXTRACTS of the plant Colchicum autumnale have been used in the treatment of acute gouty arthritis for about 1,500 years [*1*]. A large number of clinical papers have abundantly confirmed the specific effectiveness of colchicum preparations in gout but too little attention has been paid to possible mechanisms of action, to the metabolism of the drug, and to the relationship of its chemical structure to its biological effects.

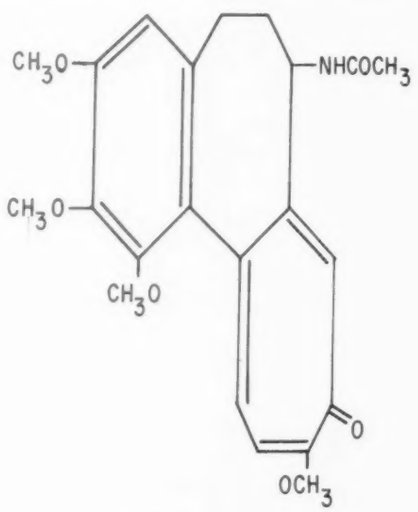
It is the purpose of this paper to review and evaluate the available studies, especially those of the last twenty years, that pertain to the pharmacology of colchicine and its effect on acute gouty arthritis, in the hope that further research to solve the many problems raised will be stimulated.

Relation of Structure to Function. Many studies over the years have dealt with the structure of colchicine; Cook and Loudon [*2*], in their excellent monograph, summarized present knowledge of its chemistry.

The chemical formula for colchicine is shown in Figure 1. It consists of three rings, the first a benzene ring, the second and third composed of seven carbon atoms. Three methoxy groups are attached to the first ring. The second ring has an acetylamino side chain, while on the third ring are a ketone and a methoxy group. Figure 2 shows the structure of some analogues of colchicine.

A preliminary study [*3*] has been made of the correlation between the structure of colchicine and some of its analogues and their effects on acute gouty arthritis. The colchicine analogues used were desacetylmethylcolchicine, desacetylthiocolchicine, colchicoside, trimethylcolchicinic acid and colchiceine. The relationship of each compound to colchicine is indicated in Figures 1 and 2. Colchicoside is a glycoside of colchicine, the sugar replacing a methyl group on the benzene ring. A methyl group is substituted for the acetyl group on the side chain of the second ring in desacetylmethylcolchicine. In desacetylthiocolchicine there are two areas of substitution: in the side chain of the second ring the acetyl group is absent, and in the methoxy group attached to the third ring sulfur replaces the oxygen. In trimethylcolchicinic acid, the acetyl group is again missing from the side chain on the second ring, and there is an hydroxy instead of methoxy on the third ring. Colchiceine most likely is a derivative of isocolchicine rather than of colchicine, and has an hydroxyl group replacing the methoxy on the third ring of that compound [*4*].

These substances were used in the treatment of acute gouty arthritis in doses approximately equimolecular to therapeutic amounts of colchicine. Desacetylmethylcolchicine, desacetylthio-



Colchicine

FIG. 1.

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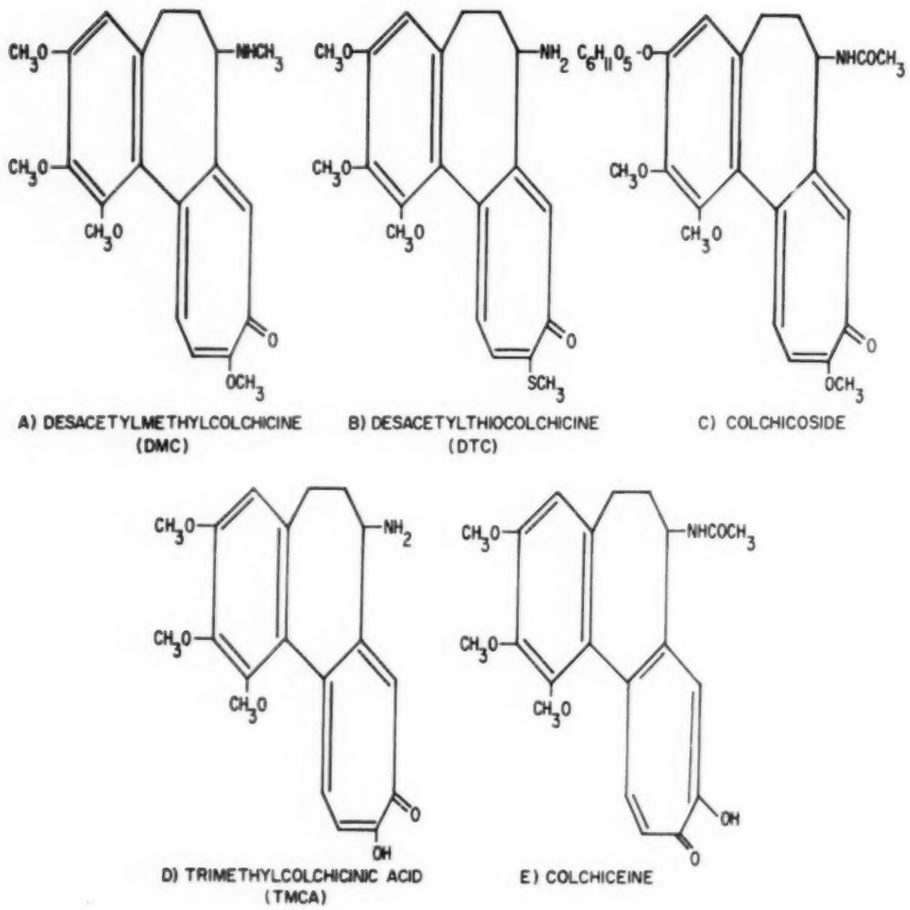

FIG. 2.

colchicine and trimethylcolchicinic acid were found to be effective, colchicoside was less potent although it retained some antigouty activity, and colchiceine was ineffective, both orally [*3*] and intravenously [*5*]. The reason for the ineffectiveness of colchiceine is not certain. Failure of absorption from the gastrointestinal tract does not seem to be a factor, since the drug is also inactive when administered intravenously. Colchiceine differs from the other, more effective analogues of colchicine by its isomeric modification in the third ring, and it is possible that this alteration in structure accounts for its lack of activity. Isocolchicine has not been tested for antigout action.

Both desacetylthiocolchicine and trimethylcolchicinic acid also have changes in the side chains of the third ring, but both are similar in spatial configuration to colchicine rather than isocolchicine. Both are effective in the treatment of acute gouty arthritis. Desacetylmethylcolchicine, desacetylthiocolchicine and trimethylcolchicinic acid also embody alterations in the side chain of the second ring without losing antigout effect. Colchicoside is the only analogue tested in which the substitution was made on the first ring; colchicoside had less activity in gout than colchicine.

The third ring of colchicine, with the attached side chains, has the configuration of tropolone methyl ether [*4,6–8*] (Fig. 3A) whereas colchiceine has the configuration of tropolone. (Fig. 3B.) Benitez and coworkers [*9,10*] have shown that although tropolone itself did not act on cell mitosis, its presence completely abolished the antimitotic effect of colchicine on rat fibroblast tissue cultures. There have been no reports of the use of tropolone or of its derivatives other than colchicine and the colchicine analogues in the treatment of acute gouty arthritis.

Metabolism. There is a delay of from three to six hours between administration of large doses of colchicine and the first signs of toxicity [*11–13*]. With the therapeutic use of colchicine

in acute gouty arthritis, joint symptoms and signs usually begin to subside about twelve hours after the institution of oral therapy, and complete relief rarely occurs before one or two days [*14*]. Intravenous administration customarily produces benefit in three to four hours [*15,16*], although one group using smaller doses of intravenously administered colchicine claimed a response in five to fifteen minutes [*17*]. The reason for the delay in appearance of the effects of colchicine is not clear, but most likely lies in the metabolism of this compound.

Comparatively little is known about colchicine metabolism, because of the difficulty in measuring colchicine in body fluids and tissues in the amounts present during the treatment of gout.

Lettre [*18*] was able to detect as little as 0.01 μg./ml. of colchicine by its action on dividing fibroblasts in tissue culture. Using this technic of biologic measurement, he found that colchicine was excreted by the liver via bile into the intestine. He found no urinary excretion, and there was no detectable amount in the brain by this method. The technic measures antimitosis alone, however, and thus groups together colchicine with all its metabolites that have antimitotic effect, while not detecting metabolites that have no such activity.

Walaszek, Geiling and their collaborators [*19,20*] prepared C^{14} labelled colchicine extracted from *Colchicum autumnale* grown in a radioactive CO_2 atmosphere. The precise location of the C^{14} labelling was not determined. In a brief abstract, they reported [*20*] giving 3 mg. of radioactive colchicine intravenously to patients with cancer, to others with gout, and to "normals" without these disorders. In most patients 70 to 97 per cent of the radioactivity appeared in the urine in forty-eight hours. Three "normals" excreted unchanged colchicine in the urine in the amounts of 15.6, 20.3 and 46.7 per cent of the administered dose. Two gouty patients excreted 3.6 and 4.7 per cent of the dose, and four patients with cancer excreted 3.9 to 6 per cent of the administered dose in the urine as unchanged colchicine. The authors did not state whether the patients with gout were in an attack when studied, nor did they give data as to renal function in these patients. If abnormal renal function is not a factor, these results imply some difference in colchicine metabolism between "normals" on the one hand and patients with gout or cancer on the other.

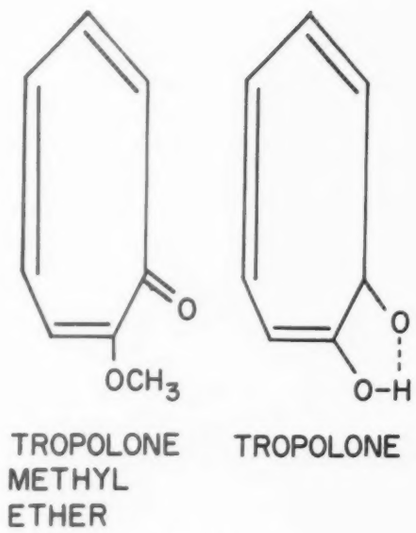

FIG. 3.

Radioactive colchicine was given to mice in other studies [*21,22*]. The animals were sacrificed after four hours. The intestine contained 18.3 to 22.8 per cent of the radioactivity at that time, the kidney 22.6 to 28.6 per cent, liver 7.4 to 15.1 per cent, and spleen 39.2 to 47.1 per cent. The heart, brain, muscle and blood exhibited no significant radioactivity. The measurements of organ radioactivity reported in these papers do not, however, necessarily represent measurements of colchicine itself.

Raffauf, Farren and Ullyot [*23*] prepared colchicine labelled with C^{14} at known positions on the side chains of the first (benzene), second and third rings. Unfortunately there have been no reports of the use of this material in the study of colchicine metabolism.

Brues [*24*] gave colchicine intravenously to mice and measured blood and tissue levels by the method of Boyland and Mawson [*25*]. In this method colchicine is first hydrolyzed to colchiceine and then measured colorimetrically by a reaction with ferric chloride in chloroform. The method is quite specific, but relatively insensitive. Brues found that in his animals colchicine rapidly disappeared from the blood. Analysis of plasma at intervals after injection showed a volume of dilution of 23 cc. in a 150 gm. rat thirty seconds after injection and 76 cc. at five minutes. Thus colchicine extended beyond the extracellular space in a minute or so. The volume of dilution exceeded that of body water within a half hour. In whole blood, colchicine rapidly distributed itself between plasma and cells in a ratio of 5:3.

Analysis of whole animal plus excreta at six hours in Brues' study [*24*] showed 80 to 100 per cent recovery of colchicine. The excretion in the urine was about 10 to 20 per cent during the period of highest blood levels. Colchicine was also excreted into the bile and directly into the intestine to a lesser extent. Reabsorption from the intestine probably occurred, and for several hours one-half to two-thirds of the injected dose appeared in the intestinal tract.

New methods for determining colchicine have been reported. Pesez [*26*] described a colorimetric determination involving the reaction of colchicine with isonicotinic hydrazide in an alkaline medium. Smolenski et al. [*27*] reacted colchicine with nitric acid, water and sodium hydroxide in sequence, producing an orange-red color. These methods are perhaps more sensitive than the reaction of colchiceine with ferric chloride [*25*], but much less sensitive than the radioactivity or tissue culture technics.

Mechanism of Action in Gout. Until the pathogenesis of the acute attack of gout is established, it is unlikely that any precise knowledge will be obtained about the mechanism of action of colchicine in this disorder. Nevertheless, a review of some of the available theories may be rewarding, at least in summarizing available knowledge and in suggesting possible areas for future investigation.

Local versus systemic action: Levin et al. [*28*] administered 1 mg. of a parenteral preparation of colchicine intra-articularly, into the involved knees of four patients with acute gouty arthritis. In three of the four the attack worsened; none were helped. These results imply that the effect of colchicine itself is not local, within the synovial space. Colchicine solutions for parenteral use are very irritating, however, causing thrombophlebitis locally in a significant percentage of patients given the drug intravenously [*16,29*]. Local chemical irritation within the joint in Levin's study may have masked any therapeutic benefit.

Influence on uric acid: Preliminary studies with N^{15}-labelled uric acid [*30,31*] some years ago were interpreted to indicate that colchicine increased the uric acid turnover rate and decreased the size of the uric acid miscible pool, apparently by decreasing the synthesis of uric acid. These results were not confirmed by other workers using similar [*32*] or other [*33,34*] technics. It is now generally accepted that colchicine exerts no significant influence on the urinary excretion, serum concentration or miscible pool of uric acid.

Recently Laster and Blair [*35*] described in human and other tissues an enzyme, designated uric acid riboside phosphorylase, which catalyzed the release of uric acid from uric acid riboside by phosphorolysis. Colchicine, when administered in large amounts, was reported partly to inhibit uric acid riboside phosphorylase but not other nucleoside phosphorylases [*35*]. The most potent inhibitor of this enzyme was uracil, and propylthiouracil also was found to be very active. There are no data as yet available relating this enzyme system to the pathogenesis of acute gouty arthritis.

Influence on adrenal function: Colchicine has long been known as one of the most potent stimuli available for the production of the "alarm" reaction [*36*]. Toxic doses are necessary, however, for producing this reaction.

Abundant data are available to deny any relationship between therapeutic doses of colchicine and changes in steroid production or excretion. Levin et al. [*37,38*] administered colchicine orally in full therapeutic amount (5 to 8.5 mg. in twenty-four hours). There was no significant change in eosinophil count, urine 11-oxysteroid content, or sweat sodium. One patient with colchicine toxicity—profound diarrhea and vomiting after receiving 24 mg. in thirty hours—did show marked depression of the eosinophil count. Robinson and co-workers [*39*] noted that oral doses of 4 to 5 mg. and intravenous doses of 2 mg. did not effect the level of circulating eosinophils or of 17-ketosteroid excretion. Other observers also noted no significant influence of colchicine on 17-ketosteroid excretion [*40,41*], 17-ketosteroid urinary fractionation patterns [*40*], 11-oxysteroid excretion [*41*], circulating 11-oxysteroids [*42*], or eosinophil count [*41,43*].

On the other hand, Wolfson [*44*] reported increases in adrenocorticotrophic hormone production in man after the administration of therapeutic amounts of colchicine. Mugler [*45*] gave 0.2 mg. of colchicine to normal and hypophysectomized rats and noted eosinopenia in both groups. In other studies [*46,47*] he gave 3 mg. of colchicine intravenously to men and noted no significant change in twenty-four-hour urinary 17-ketosteroids or 11-oxysteroids, but "dehydroandrosterone" excretion increased, on the average, more than 19 per cent. In five patients he then studied steroid excretion after

similar doses of intravenously administered colchicine on each of two consecutive days, and noted increases in both "dehydroandrosterone" and 17-ketosteroid excretion on each day.

Colchicine has no influence on other disorders that respond to adrenocorticotrophic hormone and orally administered steroids. It seems unlikely in view of the available evidence that its influence on acute gouty arthritis is mediated through the "pituitary-adrenal axis."

Antimitotic activity: The antimitotic action of colchicine was first described in 1934 [*48*]. No evidence has been adduced to show that the antimitotic and antigout effects of the drug are related. However, as Goodman and Gilman [*49*] have succinctly stated, "the law of parsimony requires that an attempt be made to correlate the action of colchicine in gout with the remarkable effects of the alkaloid on cell division."

Separation of these effects has been accomplished in an analogue of colchicine, trimethylcolchicinic acid. This compound is an effective agent in the treatment of acute gouty arthritis, about as active as colchicine [*3,50*]. Trimethylcolchicinic acid has been shown to have no antimitotic effect on chick fibroblast tissue cultures in concentrations two to ten thousand times greater than active amounts of colchicine [*51*]. No antimitotic effect on mouse sarcoma 180 was shown [*52*] in doses one thousand times larger than effective doses of colchicine. Doses of 200 mg./kg. of trimethylcolchicinic acid produced no antimitotic effect on regenerating rat liver cells [*53*] or on mouse corneal epithelium [*54*]. Chronic toxicity studies in rats receiving 2 mg./kg./day have shown no evidence of any effect of the drug on cell division [*55*].

Leiter et al. [*56*], however, administered single doses of 400, 600 and 800 mg./kg. to mice bearing sarcoma 37. These doses are respectively twice, three times, and four times the minimal lethal amounts for mice. Doses of 400 mg./kg. caused no antimitosis, but one-third of animals receiving 600 mg./kg. and one-half receiving 800 mg./kg. did show evidence of mitotic arrest.

Although trimethylcolchicinic acid when administered in very large amounts can affect mitosis, it is much less potent in this activity than colchicine; since the effects on gout and on mitosis are almost completely separable in trimethylcolchicinic acid, it seems logical to assume that they are unrelated in the parent drug.

Influence on the nervous system: Jones [*57*] suggested on speculative evidence that podagra was due to acute vasodilatation of the small periarticular vessels, analogous to erythromelalgia, and that gout involves either the vasomotor nerves or the vasomotor control center in the brain. He postulated that colchicine might have its effect on one of these locations.

Ferguson [*58*], in a study of the general pharmacology of colchicine, noted that its central nervous system activity was most marked. Vomiting produced by colchicine was prevented by barbiturate anesthesia, and the diarrhea by atropine. The vasopressor effect of large doses of colchicine was due to peripheral vasoconstriction, apparently secondary to medullary stimulation. Terminal hypothermia was noted in some animals, implying involvement of the thermoregulatory center. In some animals poisoned by large doses of colchicine paralysis of the hindquarter developed; others had tonic and clonic convulsions. Loss of pain response, of reflexes, and of ability to walk was also noted. Other investigators [*59*] found that colchicine potentiated the central nervous system effects of several hypnotic and anesthetic agents.

Mugler and Gazet du Chatelier [*46,47,60*] suggested that there were two phases, both involving the nervous system, involved in the effect of colchicine on gout. First was rapid vasoconstriction, due to potentiation by colchicine of the sympathicotropic action of epinephrine on the postganglionic fibers. At the same time, anesthesia of the sensory endings was thought to occur. The second phase supervened after several hours and involved a direct effect on the central sympathetic and parasympathetic systems, both sympathicotropic and parasympatholytic [*60*].

Despite the evidence for an effect of colchicine on the central nervous system, Sternberg and Ferguson [*61*] found no pathologic changes in the central or peripheral nervous tracts in cats and rats acutely or chronically poisoned by this compound. No colchicine was found in the brain in studies of the metabolism of this drug by radioactivity [*21,22*] or tissue culture [*18*] methods.

Influence on allergy: Acute gout has not been shown to involve consistently an allergic or sensitivity mechanism, although Harkavy [*62*] described three patients with gout in whom reactions to pollens and foods seemed of patho-

genetic significance. Mugler [*63,64*] reported that intravenously administered colchicine, in doses effective in acute gouty arthritis, gave dramatic relief from the pruritus and urticarial lesions of serum sickness, Quincke's edema and dermatitis medicamentosa. Naugler and coworkers [*65*] used colchicine and desacetylmethylcolchicine, given intravenously, in the treatment of fifteen patients with angioneurotic edema and one with Quincke's edema and noted rapid disappearance of symptoms. Rapid response in relief of vertigo of various causes [*65*] and of the pruritus of biliary cirrhosis [*64*] was also reported, and raises the question of whether colchicine is truly antiallergic. Mugler [*66*] concluded that colchicine could not be considered an antihistamine drug, since it failed to alter histamine inhibition of rhythmic uterine contractions.

Massive doses of colchicine given to experimental animals have been shown to cause significant diminution of antibody titers [*67,68*], most likely because of destruction of lymphocytes and plasma cells. In experimental serum sickness [*68*], colchicine given in doses large enough to kill five of sixteen rabbits decreased the frequency of carditis and of arteritis in comparison with the untreated group.

Influence on the gastrointestinal tract: There is no evidence that the beneficial effect of colchicine in acute gouty arthritis is related to its irritant effect on the gastrointestinal tract. Some observers [*14,69*] have implied that nausea or diarrhea is necessary to obtain the best therapeutic result. Separation of the diarrhea-producing and antigout actions of colchicine has been attained in all the effective colchicine analogues tested to date. Desacetylmethylcolchicine [*3,70,71*], desacetylthiocolchicine [*3*] and trimethylcolchicinic acid [*3,50*] produce little or no gastrointestinal disturbance. In the parent drug, colchicine, there is undoubtedly no connection between diarrhea or vomiting and therapeutic effect, except that with larger doses both are more likely to appear.

Influence on enzymes: There is at present no satisfactory evidence that gout is the end result of a specific enzyme abnormality. This is an attractive postulate, however, in view of the recent findings in other inherited metabolic diseases [*72,73*]. Colchicine has been shown to affect a variety of enzyme systems, although no data available implicate any of the systems already studied in the pathogenesis of gout. Reference has already been made to the effect of colchicine on uric acid riboside phosphorylase [*35*].

Lettre [*18*] noted an interrelationship between colchicine and adenosine triphosphate. Added adenosine triphosphate counteracted the colchicine effect on mitosis. Lettre concluded that colchicine inhibited a reaction between adenosine triphosphate and a contractile system of the actomyosin type within the cell during mitosis. Barany and Palis [*74*] found that colchicine given in concentrations of 10^{-8}M (the smallest concentration affecting mitosis) reduced the rate of decrease in viscosity in mixtures of heart actomyosin and adenosine triphosphate. Colchicine had no effect on adenosine triphosphatase activity in this dilution [*75*]. In an *in vitro* metabolic study of frog sartorius muscle, colchicine administered in concentrations of 10^{-3}M had no effect on muscle adenosine triphosphate activity [*76*].

The influence of colchicine on nucleic acid synthesis has been studied [*77*], using the rate of incorporation of C^{14}-labelled sodium formate into nucleic acids and purines of adult mice as a criterion. Lethal doses of colchicine (2.4 mg. per kilo) had relatively little effect on nucleic acid synthesis. Bloch [*78*] noted that colchicine did not directly inhibit the synthesis of desoxyribonucleic acid in cultured rat fibroblasts. Colchicine given in concentrations of 1.2×10^{-2}M did, however, inhibit dephosphorylation and deamination of desoxyribonucleotides, and also reduced activity of desoxyribonuclease [*79*].

Colchicine administered in concentrations of 10^{-2}M in rat liver slices *in vitro* [*80*] inhibited the synthesis of creatine from guanidoacetic acid and L-methionine, the methylation of nicotinamide and, to a lesser degree, the conjugation of p-aminobenzoic acid with glycine. Colchicine given to rats in doses of 1 mg. per kilo caused marked diminution in duodenal alkaline phosphatase [*81*], and decreased DOPA decarboxylase in the liver, although it had no effect on liver amine oxidase activity [*82*].

Godman [*83,84*] found that colchicine given in concentrations of 10^{-8}M or greater caused disruption of sarcoblast ribbons in tissue culture. This concentration is comparable to that inhibiting mitosis, and is much smaller than the minimal concentrations capable of inhibiting many enzyme systems. The tissue concentrations of colchicine necessary for influencing acute gouty arthritis are not known.

THERAPY

Acute Gouty Arthritis. Colchicine has both diagnostic and therapeutic value in the treatment of acute gouty arthritis. No other form of acute arthritis is known to respond to this agent. Colchicine should be given at the first appearance of the symptoms of an attack. Delay of even a few hours may increase the severity or prolong the duration of the acute episode [*14*].

A generally accepted method [*85–88*] of using colchicine diagnostically and therapeutically is to give 0.5 mg. of the alkaloid every hour or 1 mg. every two hours until diarrhea or other gastrointestinal upset occurs, or until therapeutic benefit, whichever occurs first. If neither of these appears, an arbitrary maximum dose is reached, usually 7.5 to 10 mg., roughly according to the patient's weight [*29*].

Once the aproximate therapeutic or toxic dose of colchicine is known for a given patient, on subsequent administration one-half or two-thirds of this dose may be given at once and the remainder given 0.5 mg. each hour. This may save the patient many hours of discomfort, without increasing the severity or frequency of toxicity. The purpose of giving small fractional doses of colchicine orally every hour has little to do with its therapeutic effect; the titration is aimed at minimizing toxicity. Persons vary greatly in the amount of colchicine they tolerate.

A significant number of patients with acute gout fail to respond to colchicine. Gutman and Yü [*88*] reported that 25 per cent of the patients treated adequately with colchicine showed persistence of swelling and pain, sometimes for weeks. Others have also reported failure rates of 25 per cent [*16*] and 20 per cent [*89*]. Delay in starting treatment probably plays a role in the reported high percentage of failure.

Intravenously administered colchicine also is effective in the treatment of acute gouty arthritis, and produces little or no diarrhea in the doses usually required [*15–17*].

The use of very small, repeated intravenous doses of colchicine instead of one larger total dose increases the likelihood of local venous irritation and does not seem to serve any purpose. Three milligrams of colchicine given slowly intravenously is generally adequate for an attack of acute gout and 2 mg. often will suffice.

Some of the colchicine analogues have been used in the treatment of acute gouty arthritis. Of thirty-four patients given trimethylcolchicinic acid orally [*50*], twenty-six responded well. Of the eight failures, three responded to the administration of additional colchicine; four were resistant to this therapy also. No significant gastrointestinal symptoms or other toxicity were noted. Desacetylmethylcolchicine is another analogue of colchicine that has been used in the treatment of acute gout, both orally [*70,71, 90*] and intravenously [*91*]. It is also about as effective as colchicine, and produces little or no diarrhea, nausea or vomiting. Bone marrow depression and loss of hair [*3,71,90*] have been caused by this agent, however; its antimitotic tendency in man is much greater than that of colchicine.

Interval therapy: Colchicine given in small doses several times a week or daily has been shown empirically to exert a prophylactic effect in recurrent acute gouty arthritis [*14,29,88*], reducing the frequency of attacks and in some cases preventing recurrence altogether. The usual dose ranges from 0.5 mg. every other day to 2 mg. daily. In sensitive subjects the larger prophylactic doses may, after one or two weeks of therapy, lead to gastrointestinal side effects. The proper dose for a given patient cannot be calculated in advance; it must be worked out by trial and error.

Toxicity. The gastrointestinal effects of colchicine are well known. Hyperperistalsis, diarrhea, nausea and vomiting occur in almost all patients to whom enough colchicine has been given. These effects may be prolonged, debilitating and difficult to control.

Patients vary significantly in sensitivity to these effects of colchicine. Deaths have been recorded after doses no larger than those used in the clinical treatment of acute gout. McLeod and Phillips [*92*] described a patient who died after receiving only 7 mg. in four days, most likely due to shock and dehydration following colchicine-induced diarrhea and vomiting.

Other toxic manifestations from relatively small doses of colchicine have been reported. Seed and co-workers [*93,94*] gave colchicine to patients with inoperable cancer. One patient received 12 mg. in four days. Vomiting, diarrhea, fever and prostration followed. Subsequently leukopenia, anemia and a bleeding tendency occurred. Two other patients were given 28 mg. of colchicine in seven days and 21 mg. in nine days, respectively. In both leukopenia and loss of hair occurred. All three patients died.

Fifteen milligrams of colchicine taken suicidally [*13*] produced, in addition to gastrointestinal disturbances and leukopenia, neurologic changes, including absent reflexes, positive Babinski test, loss of sphincter tone and muscle weakness. These changes are similar to some of those seen by Ferguson [*58*] in acute animal toxicity experiments. Toxic effects of such severity must be very rare, considering the extensive use of colchicine in patients with gout.

Smaller doses of colchicine, of the order of 1.5 to 2 mg., given subcutaneously or intramuscularly to human subjects with cancer have produced typical changes of metaphase arrest in the tumors [*95,96*]. It is not certain whether such small doses effect similar antimitosis in normal tissues. There is no evidence that colchicine is in itself carcinogenic [*97*].

CONCLUSIONS

It is evident that there are many gaps in our knowledge of the clinical pharmacology of colchicine in gout. Further studies on its metabolic fate in man and its mechanism of action in acute gout are needed.

Modifying the colchicine molecule on the side chains of the first (benzene), second or third rings does not abolish antigout activity, as long as the spatial configuration in the third ring conforms to that of the parent drug. Colchiceine, a derivative of isocolchicine, has side chains on the third ring with different spatial arrangements from those of colchicine; it is ineffective in the treatment of acute gout.

Colchicine given orally is absorbed in the gastrointestinal tract, passes through the liver, and re-enters the intestine by way of the biliary tract. Some is reabsorbed from the intestine. Urinary excretion of unchanged colchicine is reported by some but denied by others. In any event, colchicine disappears very rapidly from the blood, and is not measurable in the brain, heart or muscle.

The mechanism of action of colchicine in acute gouty arthritis is as poorly understood as the pathogenesis of the attack itself. Colchicine, when given in therapeutic doses, does not seem to have any significant effect on uric acid metabolism or on adrenal cortical function. As far as can be determined, its antigout activity is not related directly in any way to its antimitotic effects, nor is it dependent upon the production of diarrhea. The drug has been shown to have a distinct action on the central nervous system. In sufficient concentrations it affects a variety of enzyme systems. It is possible that its potent antigout action is related to one of these areas.

The use of colchicine, both orally and intravenously, has been reviewed. Desacetylmethylcolchicine, an analogue of colchicine, has been shown to be both effective in acute gouty arthritis and more toxic than the parent drug. Trimethylcolchicinic acid, another analogue, is both effective and non-toxic when used in therapeutic dosages.

Finally, colchicine has been shown to have toxicity in addition to its well known gastrointestinal side effects. In sensitive subjects, leukopenia, bone marrow depression, loss of hair, nerve damage and death have been reported to follow doses little larger than those used in the treatment of gout in some patients. Such reactions, however, have been rarely encountered.

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Combined Staff Clinic

The Effect of Mitral Commissurotomy on the Natural History of Rheumatic Heart Disease

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Nicholas P. Christy.

DR. DANIEL L. LARSON (CHAIRMAN): There is a paucity of information in the literature concerning the natural history of rheumatic heart disease, particularly mitral valvular disease in the adult. One thing is clear, however, that the natural history of rheumatic heart disease in the adult is changing remarkably, and that the picture of the disease as presented in many textbooks may be misleading with respect to the present status. The two most significant factors, perhaps, in this change are (1) the subject of this clinic, namely, interference by surgical measures, and (2) the use of antistreptococcal prophylaxis. (The latter factor will not be discussed in this clinic.)

One thing that is not sufficiently emphasized in many discussions of rheumatic fever is the relative infrequency with which significant mitral valvular disease ensues after an attack of acute rheumatic fever. Consider, for example, the classic study of the natural history of rheumatic heart disease carried out by the late Duckett Jones in Boston [*1*]. He collected the records of a thousand children, average age eight years, who had rheumatic fever or chorea and studied their courses over a twenty-year period. To be sure, this group of patients is not entirely comparable to the group we are going to discuss. For one thing, the average age of the patients at the termination of the Jones' study was twenty-eight, which is considerably younger than those in the group we are going to talk about. Another consideration is that the children in the Boston study were not maintained on antistreptococcal prophylaxis. Further, we have no information as to the number and type of recurrences of rheumatic fever which they sustained. Be that as it may, over the twenty-year period, significant murmurs vanished in 16 per cent of the patients. In 44 per cent of the patients new murmurs occurred, presumably in relation to renewed rheumatic activity. Of particular interest are the 117 persons in whom mitral stenosis developed and who were long-term survivors. On the basis of roentgenographic data, only about 10 per cent of these patients had evidence of pulmonary hypertension. This is the group that might become candidates for mitral commissurotomy at the present time and the low percentage emphasizes the relatively small proportion of patients with mitral disease who really qualify for the operation.

Another follow-up study, carried out at the New York Hospital [*2*], is in some respects more comparable to the group that we are going to discuss. In the New York Hospital study, 269 children with a documented attack of carditis were followed into the third, fourth and fifth decades of life. In about 75 per cent of those with mitral disease, the diagnosis of mitral stenosis became apparent within two years after onset of the disease, at a time when they were still children. Of considerable interest is the fact that the murmur of mitral stenosis regressed in approximately two-thirds of the patients, and the murmur of mitral insufficiency regressed in about one-third. This phenomenon is of some importance in consideration of the persons who have so-called "pure" mitral stenosis. It was rare in this study to detect the appearance of a new murmur in the absence of renewed rheumatic activity. Cardiomegaly was present in 20 per cent but, in the absence of a new attack of acute rheumatic fever, there was rarely any increased enlargement of the chambers. It was observed that the events which we commonly see in rheumatic patients on the wards, such as atrial fibrillation, thromboembolic disease, subacute bacterial endocarditis and severe congestive heart failure, are relatively rare compli-

cations of mitral stenosis, culled from the very much larger group of the rheumatic population as a whole. So far as functional impairment is concerned, only 11 per cent of this large group of people had any significant cardiopulmonary symptoms. Again, this rather clearly defines the relatively small proportion of people with mitral stenosis who might be considered candidates for mitral commissurotomy.

So much for the general background of our misconceptions concerning the natural history of rheumatic heart disease. We have had an opportunity to study a group of people at the Presbyterian Hospital who have undergone mitral commissurotomy. Dr. Dorothy Estes will describe some of the findings in these patients. It will become apparent that the data are in substantial disagreement with certain other reported studies of the results of mitral surgery.

Dr. Dorothy Estes: As Dr. Larson has indicated, this study has been in progress for the past two years. We have attempted to determine the long-term effects of mitral commissurotomy and to define the criteria for selecting the patients who will benefit by the procedure. The doctors participating in this study have been Dr. Larson, Dr. Tor Richter and myself.

There are three ways of conducting such a study: (1) the patient questionnaire system, (2) direct clinical appraisal, or (3) cardiac catheterization.

In the first method, which has been used in some of the larger studies, patients fill out questionnaires about once a year and these are reviewed by the investigating physician. This system stresses the more subjective nature of patients' complaints, and may often be misleading. Patients who have endured the emotional, physical and financial trauma of cardiac surgery may find it difficult to admit to themselves and to others that they have not been improved. In the present study, eighty patients stated they felt better. However, after more careful clinical appraisal by a physician, only two-thirds of these eighty were found to be really improved.

On the other hand, a patient who has used his cardiac disease as a psychological crutch for many years may find it equally difficult to admit that he is improved. As an example, one patient in this study was operated on because of hemoptysis and congestive heart failure which limited her activities to a moderate degree. Since operation, this patient has had no hemoptysis nor has she shown any evidence of congestive heart failure. Yet, she describes herself as worse, a cardiac invalid confined to bed. However, it is known that this patient leads a very active social life.

We have ourselves used the method of direct clinical appraisal. Patients have been seen about once every six months by one of the three doctors participating in the study. At each visit the patient was questioned carefully about changes in symptoms, activities and limitations, medications, and other major medical events that may have occurred, such as emboli. The physical findings were recorded after each visit. Electrocardiograms and chest roentgenograms have been obtained once a year. In this way it was believed that the psychological factor in patients' complaints could be minimized, and other factors which might affect the clinical state of the patient, apart from the effect of the mitral commissurotomy, could be recognized.

The third method, cardiac catheterization, has been employed in further evaluating several of the patients in this study. Dr. John Wood has had an opportunity to evaluate these patients preoperatively and postoperatively by measuring right heart pressures and flows, and will report on his findings later.

The specific objectives of this study were to determine (1) the number of patients benefited by the operation, (2) the effects of commissurotomy on the complications of rheumatic heart disease, specifically, atrial fibrillation, congestive heart failure, embolic phenomena and bacterial endocarditis, (3) the mortality and causes of death in the operative and postoperative periods, and (4) the criteria for selecting patients for mitral commissurotomy.

A total of 147 operations have been performed on the ward service between 1950 and 1958, inclusive. Seventeen of these patients are considered lost to follow-up. We have heard from the majority of these and know they are alive, but they have not been included. This study comprises the remaining 130 patients. The length of follow-up has been from three months to eight years, with an average of forty-six months. The patients ranged in age from twenty to sixty years, with a mean age of thirty-nine.

After each clinic visit, patients were classified as "improved," "unchanged" or "worse," according to the following criteria: (1) a change in exercise tolerance, (2) the need for medical therapy, (3) the state of cardiac compensation, (4) emboli, (5) hemoptysis, and (6) change in

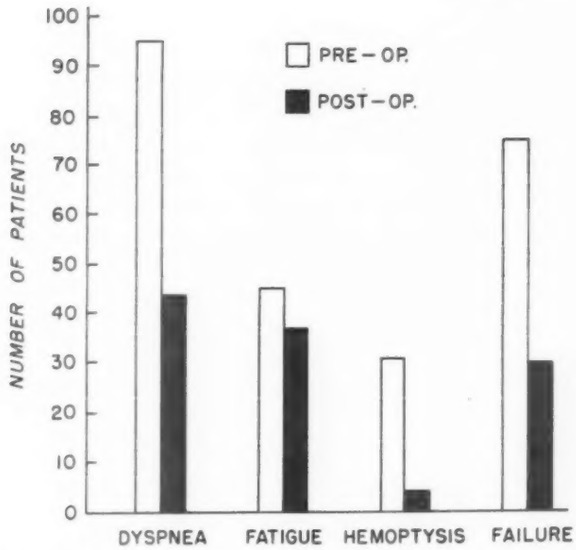

FIG 1. Effect of mitral commissurotomy upon the gross features of rheumatic heart disease (changes in preoperative symptoms during the follow-up period in ninety-nine patients).

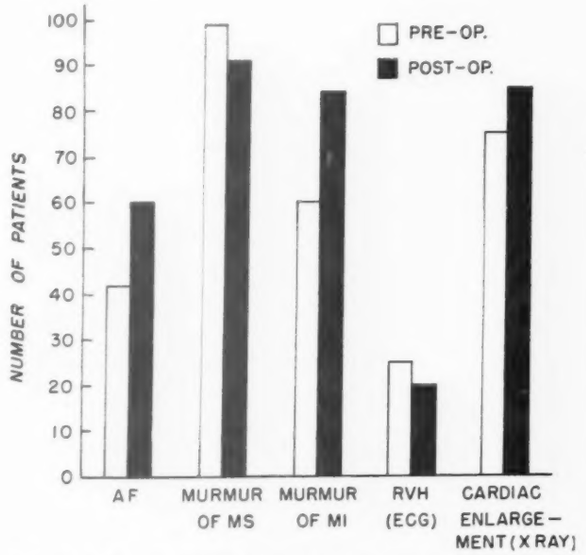

FIG. 2. Effect of mitral commissurotomy upon objective physical and laboratory signs of rheumatic heart disease (changes in preoperative and cardiac signs during the follow-up period in ninety-nine patients).

cardiac size or in electrocardiographic findings. If any one of these factors were changed toward improvement, it was designated by a plus sign; changes toward deterioration were indicated by a minus sign. The sum of these positive and negative signs represented the final evaluation for each patient.

For example, one patient was operated on because of severe congestive heart failure which precluded his working. Since commissurotomy this patient has had no congestive heart failure and now works full time. He has been classified as "improved." A second patient was operated on because of congestive heart failure of milder degree. At the time of surgery this patient had a cerebral embolus. The resulting hemiparesis has limited her to an equal degree. Other factors have remained unchanged. She has been classified "unchanged." A third patient was operated on because of a femoral embolus. Since operation, this man has had no emboli. However, congestive heart failure of severe degree has developed, despite increasing medication. He has been classified as "worse."

The current status of these 130 patients is as follows: fifty-seven patients, or 44 per cent, have been classified as "improved"; twenty-eight, or 21 per cent, have shown no change; fourteen, or 11 per cent, have been classified as "worse"; and thirty-one patients, or 24 per cent, in this series have died.

Figure 1 summarizes the changes that have occurred in the ninety-nine living patients. Hemoptysis has been the most strikingly decreased manifestation. Of four patients having hemoptysis now, three also had it preoperatively. In one it has developed for the first time since surgery. The incidence of congestive heart failure has been decreased by about 60 per cent, and that of dyspnea by about 50 per cent. Fatigue has been little altered.

Figure 2 summarizes the more objective changes that have occurred in these patients. In seventeen patients atrial fibrillation has developed since surgery. The murmur of mitral stenosis has remained in most of the patients. Sixty patients had a mitral systolic murmur prior to surgery. Since operation, a mitral systolic murmur of grade 2 severity or greater, or an upgrading of two gradations of this same murmur, suggesting the development of mitral insufficiency, has developed in twenty-four patients. At the same time, twelve patients have had a decrease or loss of a mitral systolic murmur. Electrocardiographic indications of right ventricular hypertrophy have reverted toward normal in only five patients. Seventy-five patients showed cardiac enlargement of some degree on chest roentgenograms before surgery. Since operation, ten patients have had a substantial increase in transverse cardiac diameter. Only three patients have shown a comparable

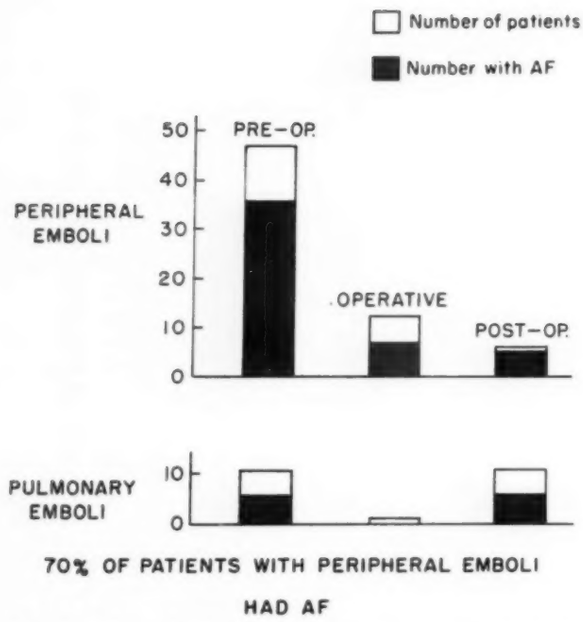

FIG. 3. Effect of mitral commissurotomy upon the incidence of embolic phenomena and fibrillation in 130 commissurotomized patients with rheumatic heart disease. The frequency of peripheral emboli is reduced, whereas that of pulmonary emboli is unchanged.

decrease. Thus, changes in the objective findings have been less dramatic than the changes in symptoms. (Fig. 1.)

Of the thirty-one patients in this series who have died, 13 per cent died during the period of follow-up and 11 per cent during the operative period. However, if the operative mortality is broken down into the first five years the operation was performed and the past four years, during the latter period this has been decreased to 7 per cent.

Mortality was further analyzed according to the preoperative cardiac functional classification. For those who are unfamiliar with the New York Heart Association cardiac classification, a class I patient is a patient with cardiac disease who is asymptomatic at any level of activity. A class II patient becomes symptomatic on moderate to severe exertion. A class III patient becomes symptomatic on mild exertion. A class IV patient is symptomatic at rest. The mortality for class IV patients was very high (64 per cent).

The major causes of death have been emboli (eleven cases), congestive heart failure (nine cases) and bacterial endocarditis (three cases). There have been three miscellaneous deaths in the postoperative period. One patient died of a cocaine sensitivity reaction while being prepared for a left heart catheterization during diagnostic study for possible restenosis of the mitral valve. The second patient died of renal insufficiency, possibly due to chronic pyelonephritis or renal emboli. No autopsy was performed. The third patient died of an acute gastrointestinal hemorrhage, secondary to a peptic ulcer.

The incidence of peripheral emboli has been markedly reduced in the postoperative period. (Fig. 3.) However, twelve peripheral emboli occurred at the time of surgery, and seven of these proved fatal. It has been the impression of some investigators that patients who have had peripheral emboli prior to surgery are more apt to have them at the time of operation. However, in this study, only three of the twelve patients who had emboli at operation gave a history of a previous embolus. The majority of patients who had peripheral emboli also had atrial fibrillation. The incidence of pulmonary emboli has been unchanged following mitral commissurotomy. There was one pulmonary embolus at the time of surgery which proved fatal.

The incidence of bacterial endocarditis doubled in the postoperative period. In five patients, positive blood cultures were obtained within five weeks of operation. The organism recovered in three of these cases was Staphylococcus aureus. The time of onset and the organisms recovered suggest that these cases were related to the operative procedure.

One of the major difficulties concerning mitral commissurotomy has been the selection of patients who will benefit by the procedure. In order to determine which of the clinical manifestations present preoperatively might have an adverse effect on the surgical outcome, certain factors were analyzed for each of the four groups of patients, i.e., those classified as improved, unchanged, worse, and those who have died. The manifestations considered were congestive heart failure of moderate to severe degree, emboli, atrial fibrillation, hemoptysis, the presence of mitral insufficiency or aortic murmurs or both, right ventricular hypertrophy evident on the electrocardiogram, and cardiac enlargement on roentgenograms exceeding 20 per cent. This type of analysis proved disappointing. There was only one significant finding, namely, that 71 per cent of the patients who died had had moderate to severe congestive heart failure prior to surgery. There was no real difference with respect to congestive heart failure among the patients in the improved, unchanged or

worse groups, and this complication was present in about 29 per cent in each of these categories.

Operative findings, analyzed in the same way, were calcification of the mitral valve, the valve opening achieved at surgery, the pathological diagnosis of carditis, and development of the postcommissurotomy syndrome in the postoperative period. The one significant finding was that 77 per cent of the patients who died had mitral valvular calcification whereas the survivors averaged about 33 per cent. It was interesting to note that the valve opening achieved, as estimated by the surgeon, had little correlation with the functional outcome of the operation. The diagnosis of carditis made by the pathologist on the auricular appendage did not adversely affect the operative outcome, nor did the development of the "postcommissurotomy syndrome" during the postoperative period.

As this type of analysis failed to indicate which patients might or might not be improved by the operation, it was decided to analyze the data further, according to combinations of adverse factors present in the preoperative period. The factors considered were age of forty-five or over, severe congestive heart failure, atrial fibrillation, disease of another valve in addition to the mitral valve, roentgenographic evidence of cardiac enlargement greater than 20 per cent, and calcification of the mitral valve. The analysis showed that when four or more of these adverse signs were present preoperatively, 80 per cent of the patients were unchanged, worse or dead. However, a few of these "poor risk" patients have been improved. On the other hand, when one or no adverse sign was present, although most of the patients were improved, a small but definite surgical risk still existed. The majority of the patients in this category who died either had peripheral emboli at the time of surgery or death was caused by early surgical errors.

In summary, this study has shown, on critical analysis, that a substantial number of patients can be benefited by mitral commissurotomy. The study as presented does not take into account those patients who may have had an initial improvement following surgery and then deteriorated. There has been a definite reduction in the incidence of hemoptysis, congestive heart failure and peripheral emboli. Atrial fibrillation has continued to appear in the postoperative period, suggesting progression of myocardial damage. Subacute bacterial endocarditis occurred in high incidence in the immediate postoperative period, and may have been related to the surgical procedure.

The over-all mortality figure was high. The operative mortality, however, has been decreased by 50 per cent in the last four years. Emboli and congestive heart failure were the major causes of death in the operative and follow-up periods.

One may conclude that patients with severe long-standing congestive heart failure, calcification of the mitral valve, and the majority of those in cardiac classification IV had a high mortality rate. In addition, patients who had four or more adverse signs preoperatively were seldom improved. Stated another way, the ideal candidate for mitral commissurotomy would be a person under forty-five years of age who has a small heart in regular sinus rhythm, in whom there is no radiological evidence of valvular calcification, and in whom there are definite signs of recent deterioration.

DR. LARSON: It would be of considerable interest to learn whether or not those patients who have symptomatic improvement following mitral commissurotomy show not only an initial drop in their pulmonary artery pressure but also a sustained lowering of pressure on catheterization of the right side of the heart after a relatively long period of time. Dr. Wood has had the opportunity to recatheterize several patients who have been followed up for several years after operation. He will now tell us about his results.

DR. JOHN A. WOOD: From 1950 to 1953, with the late Dr. John West, eighteen patients with rheumatic mitral stenosis were catheterized in the Cardio-Pulmonary Laboratory of the Presbyterian Hospital prior to and following mitral commissurotomy. On the basis of the physiological data obtained, thirteen of these patients were classified as "improved," two as "unimproved," and in three the results were equivocal. During the Fall of 1959 the course of these patients was reviewed with Dr. Estes. We found that, since the initial study, six had died: three of congestive failure, one of possible pneumonitis, one was the patient mentioned by Dr. Estes as sensitive to cocaine, and one of unknown causes.

Ten patients of the remaining twelve maintained their clinical improvement, as indicated by Dr. Estes' analysis. One patient was unimproved, and one was lost to follow-up. It is in this group of ten that we have attempted to collect physiological data to confirm or deny the benefit that Dr. Estes observed clinically.

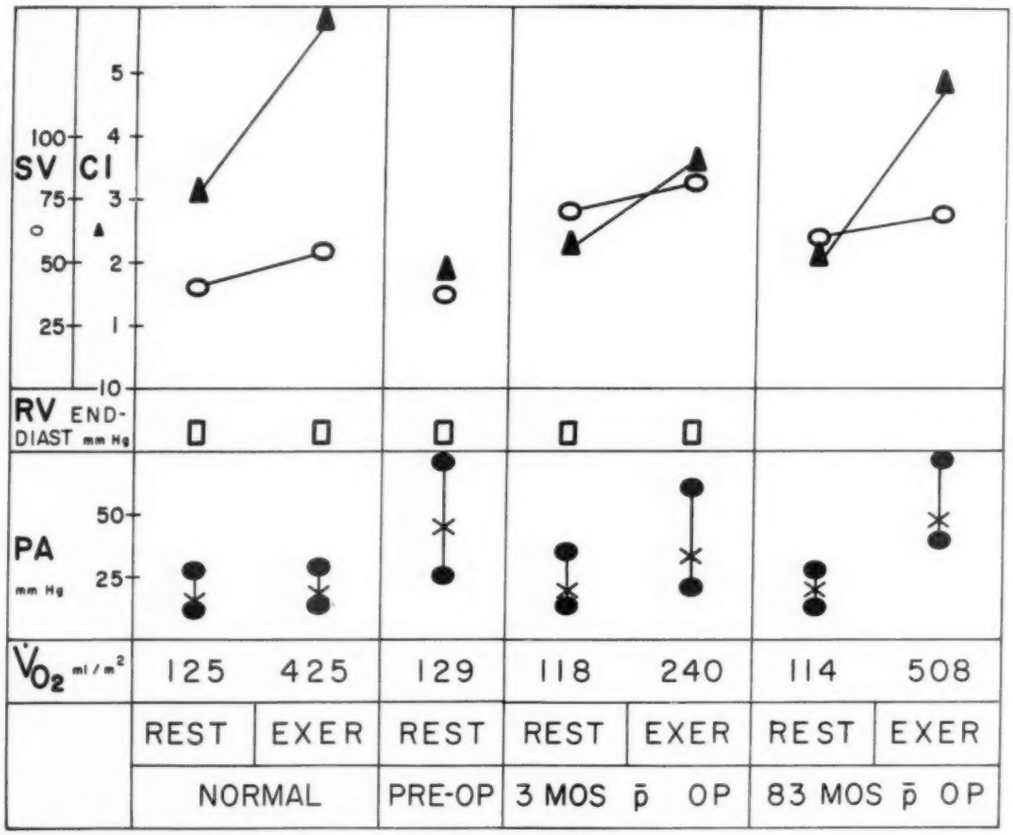

FIG. 4. Physiologic data obtained in patient W. M. by right heart catheterization before, shortly after, and long after mitral commissurotomy. Similar results were found in three additional patients. Abbreviations: SV = stroke volume, CI = cardiac index, RV end-diast = right ventricular end-diastolic pressure, PA = pulmonary artery pressure, $\dot{V}_{O_2}$ = oxygen uptake. Values for normal subjects as well as for the patient are given. Changes on exercise in the normal are predicted (calculated) on the basis of an oxygen uptake on exercise roughly equivalent to the oxygen uptake actually achieved during exercise by the patient when studied eighty-three months after operation. After commissurotomy, pulmonary artery pressure fell and cardiac index rose, improvements which persisted long after surgery, but the abnormal increase in pulmonary artery pressure on exercise remains.

With the help of Drs. Robin Briehl, Mario Rigatto, Martin Tuller and David Lehr, six patients (five improved and one unimproved) were recatheterized during the Fall of 1959, seventy-four to 108 months following mitral commissurotomy. Rather than attempt to present the mass of accumulated data here, it would be better to discuss the findings in two patients who may be regarded as typical of the group as a whole.

In Figure 4 the data obtained on patient W. M. are considered in detail and the pattern formed by the clinical and physiologic data in this patient may be regarded as typical of three other patients in this series.

When first seen, patient W. M. was a forty-seven year old white longshoreman who complained of severe exertional and paroxysmal dyspnea and hemoptysis, and was unable to work because of the severity of his symptoms. Clinically, he suffered from a relatively pure mitral stenosis. On roentgenographic examination his heart was enlarged moderately and the electrocardiogram revealed normal sinus rhythm and right ventricular hypertrophy.

Prior to his operation, the pulmonary artery pressure was quite elevated, 72/26, and his cardiac index was rather low. At operation the mitral valve was found to be markedly stenosed and a mural thrombus was noted in the left atrial appendage. No calcification was present. The valve was fractured to 2½ fingerbreadths. The patient tolerated the procedure well.

He was catheterized again two and a half

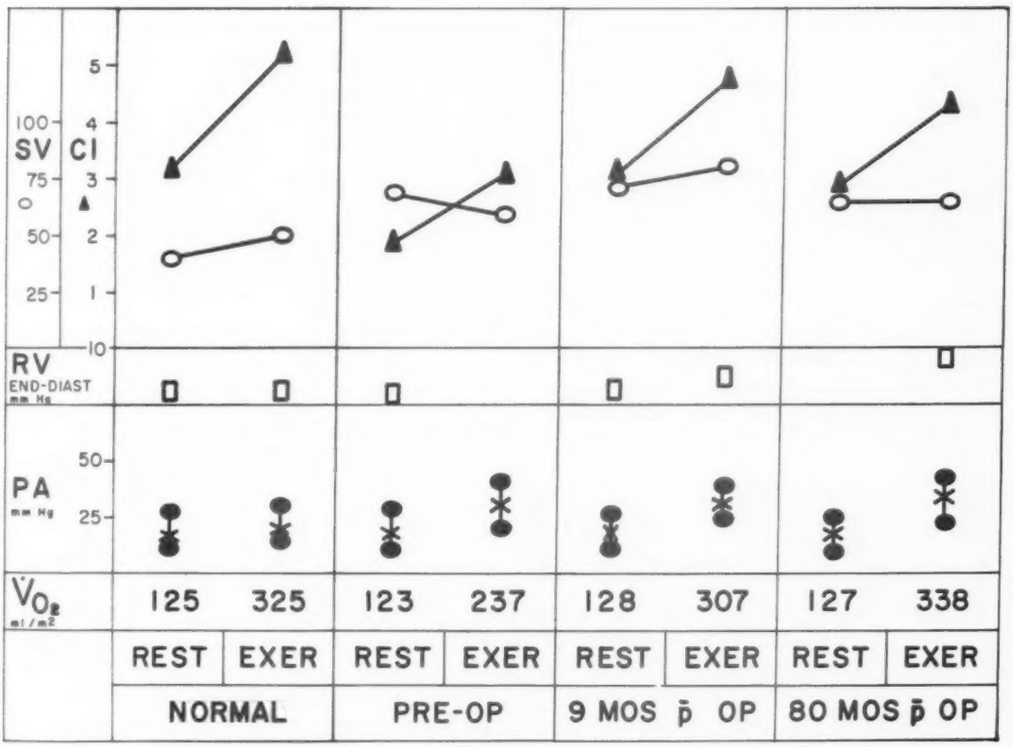

FIG. 5. Physiologic data obtained from patient A. L. by right heart catheterization. For abbreviations and calculated effects of exercise, see text and legend for Figure 4. As in the patient shown in Figure 4, physiologic improvement was maintained nearly seven years after commissurotomy.

months after operation and the results are shown in Figure 4. There is a marked fall in his pulmonary artery pressure and a rise in his cardiac index. The postoperative resting oxygen consumption is about the same as it was prior to operation. However, on rather mild exercise there was a definite rise in the cardiac index, at the expense of a rise in his pulmonary artery pressure. This suggests either some degree of residual mitral stenosis or some increase in the pulmonary vascular resistance. Clinically, he was greatly improved and able to work successfully as an oiler on a tramp steamer. X-ray examination showed that his heart was smaller than it had been preoperatively but still larger than the predicted normal size. The electrocardiogram remained unchanged.

In the seven years that have elapsed since operation, this patient has been working chiefly as a longshoreman, with good exercise tolerance and no further paroxysmal nocturnal dyspnea or hemoptysis. His heart has not changed in size, and his electrocardiogram still reveals a pattern of right ventricular hypertrophy. The third catheterization was performed eighty-three months after mitral commissurotomy and the results are quite similar to those which were obtained two and a half months after mitral commissurotomy. Again note the very good increase in his cardiac index, suggesting good myocardial function. However, a rise in pulmonary artery pressure on exercise persists.

Figure 5 shows a second type of response to mitral commissurotomy. This woman (A. L.) was a forty-two year old white married telephone operator, who was told of a heart murmur during her first pregnancy, at the age of twenty. Her postpartum period was complicated by bouts of paroxysmal nocturnal and exertional dyspnea, but then she was free of symptoms for five years. The decade following this asymptomatic period was characterized by bouts of edema of the ankles, exertional dyspnea and episodes of palpitations and substernal pain, and punctuated by renal, cerebral and splenic infarcts. Atrial fibrillation began at age thirty-six and persisted. Preoperatively, roentgenograms revealed that her heart was 20 per cent enlarged, and the electrocardiogram showed atrial fibrillation and evidence of diffuse myocardial disease, but no right ventricular hypertrophy.

Cardiac catheterization was performed, with

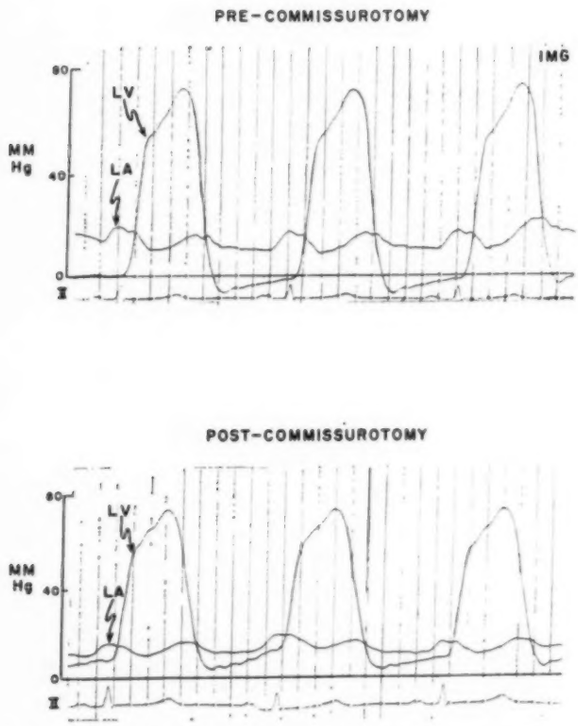

FIG. 6. *Top*, physiologic data obtained at operation (left heart pressure pulses in mitral stenosis) by direct left atrial puncture (LA) and arterial puncture (LV). (II = standard lead II of the electrocardiogram.) *Bottom*, note the great postoperative reduction in pressure gradient across the mitral valve, i.e., closer approximation of LA to LV curve after commissurotomy, especially during diastole and onset of ventricular systole. (Reproduced by courtesy of Drs. A. P. Fishman and A. G. Jameson who obtained these pressure tracings).

the results shown in Figure 5. Normal values at rest are indicated in the first column, and the expected effects of exercise have been calculated, using an oxygen consumption in the same range as that achieved by the patient during her most recent study. This patient differed from W. M. in that her resting pulmonary cardiac pressure was normal and she had a very low cardiac index. On exercise, there was some rise in pulmonary artery pressure, accompanying a modest rise in cardiac index. This pattern is somewhat unusual as an indication for mitral commissurotomy and the chief factor for the decision favoring operation in this case was the presence of recurrent arterial emboli. At operation, the valve was markedly stenotic but was flexible and without calcification. A slight regurgitant jet was noted. A 2 fingerbreadth opening was achieved.

Following operation, catheterization showed that the pulmonary artery pressure was normal but the cardiac index was just about the same as that which the patient had achieved on exercise preoperatively, and that at this increased rate of flow, the pulmonary artery pressure was normal. During exercise, a good increase in cardiac index occurred but her pulmonary artery pressure rose somewhat.

Clinically, the patient noted a marked increase in her exercise tolerance and in her ability to perform work; and no further bouts of paroxysmal nocturnal dyspnea or emboli occurred. Her electrocardiogram has remained unchanged from its preoperative appearance, and her heart size has increased, compared with that noted preoperatively.

Cardiac catheterization performed eighty months after operation indicated that her physiologic improvement has been maintained, although some residual stenosis or increased pulmonary vascular resistance remains.

In reviewing this laboratory's long-term experience with mitral stenosis and correlating it with that published by others, an assessment of the clinical usefulness of cardiac catheterization in mitral stenosis seems possible. On the whole, the clinical criteria suggested by Dr. Estes seem completely adequate in appraising the patient with straightforward mitral stenosis. The complaints of exertional dyspnea and hemoptysis correlate well with the presence of pulmonary hypertension, and caution must be exercised primarily when congestive heart failure or roentgenographic evidence of valvular calcification is present. We consider that arterial embolization is in itself a prime indication for operation. When the physician has doubt as to the patient's reliability as a reporter or when he cannot assess the relative value of mechanical obstruction versus myocardial insufficiency in producing the patient's symptoms, right heart catheterization may be useful in demonstrating the presence of pulmonary hypertension and in determining the physiologic pattern of response to exercise.

On the other hand, in the face of mitral insufficiency or multiple valvular disease, right heart catheterization has little, if any, value. The direct measurement of the pressure gradient across the mitral valve is of critical importance in these more difficult cases, and it is here that left heart catheterization has real value.

The data in Figure 6 were obtained in the operating room by Drs. A. P. Fishman and A. G. Jameson. The data presented in Figure 6 (top) were obtained prior to mitral commissurotomy

by direct left atrial puncture. In all phases of diastole and particularly near the onset of ventricular systole, there is a distinct gradient across the mitral valve. Figure 6 (bottom) shows the tracings that were obtained following mitral commissurotomy in this patient. The mitral gradient has been greatly reduced, demonstrating the successful removal of valvular obstruction in this patient.

Although the current technics for measuring the mitral gradient are difficult and at times hazardous, the need for such information justifies a continued effort to develop adequate, safe technics for measurement not only of the pressure gradient but also of the flow across the mitral valve at the time the pressure gradient is measured.

DR. LARSON: In an attempt to resolve the problem of which patients are most apt to benefit by mitral commissurotomy, another physiologic study has been carried out by Drs. Ferrer and Harvey. Dr. Ferrer will now present the results of their work.

DR. M. IRENÉ FERRER: As many of you are aware, this material was gathered at the Bellevue Hospital, and Dr. Harvey and I have had the opportunity of working with this group of patients for the past ten years.

In the course of considering the various factors which disturb the circulation in rheumatic heart disease, we have found it useful to look at the possible variations from a very simple point of view, namely, the possible mechanical and myocardial features which must be investigated. Looking at the problem schematically, patients with rheumatic heart disease may follow two pathways. The first is characterized predominantly by valvular involvement. These patients (in particular, those having mitral valvular disease with stenosis) may have no impairment in the flow across the valve or they may have mitral block. This is the group with which we are here primarily concerned. Some of those with mechanical block may at times move into the group with myocardial failure but they usually come out of failure in a fairly reasonable time. The second pathway is represented by patients with no mechanical block but rather with predominantly myocardial involvement. We know very little of the details of the myocardial factors but we do know that these people, dynamically speaking, possess a form of disturbed circulation to which we have given the term "myocardial insufficiency" or "hypodynamic performance," and that they have chronic or repeated bouts of congestive failure.

During the first five years that mitral commissurotomy was available, we at Bellevue dealt with sixty candidates who had been carefully selected by their physicians and referred to us as suitable by the then existing criteria, which were entirely clinical. Of course, we rejected fifteen simply on clinical grounds; ten were found to have active rheumatic carditis and five had subacute bacterial endocarditis previously undetected. Fifteen more were rejected after cardiac catheterization, and for the following reasons: Nine of them, in our opinion, had evidence that the myocardium was primarily at fault; two had very minimal pulmonary hypertension and, since this was associated with symptoms that were not clear-cut, we rejected them as well; four had no physiologic abnormalities in spite of their symptoms; three, at the last moment, decided not to accept our recommendation for surgery. And so we ended up with twenty-seven subjects who underwent mitral commissurotomy.

An evaluation of the surgical results was made at the end of the first five years and again nine to ten years postoperatively. In the beginning, we had what we thought were eight excellent and five good results, thus involving about half of the patients operated. We had some (three patients), as did Dr. Estes, in whom there was no change postoperatively. We had, as was true in all clinics at the beginning of this form of surgery, a considerable number of operative deaths (five patients), and six who died later had had no early change. The results are different now. Four of the original eight patients with excellent results have remained excellent and one is still a good result; three of them, however, are concerning us considerably, two because they are showing clinical deterioration and one because he has pulmonary artery pressures which have begun to rise again.

Of the original five patients with good results, three are as before but two have died. Of the three who showed no early change, two are now worse, and one is psychotic and hence difficult to assess.

In summary, we think that about a third of our twenty-seven patients have shown improvement in the long run (as of 1960) as compared to thirteen of twenty-seven in 1955. I should remind you, of course, that this is a small study and that nowadays, with the help of the hemodynamic

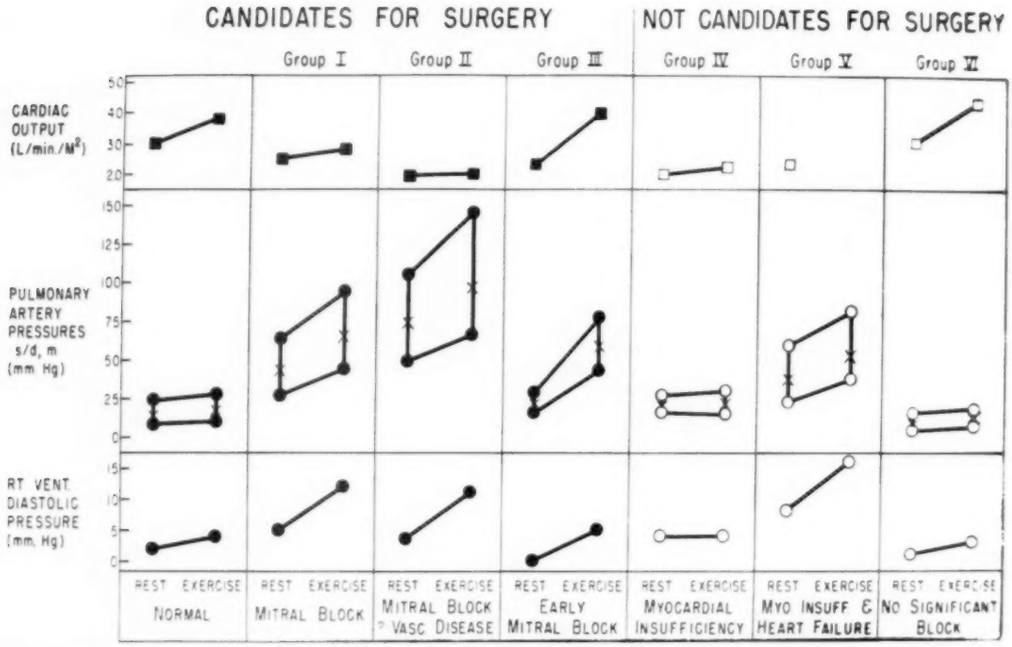

FIG. 7. Hemodynamic data at rest and during supine leg exercise in six groups of patients with mitral stenosis. Each group is represented by a study of a single patient, typical of the group. (Reproduced by permission of the American Heart Association, Inc. From: HARVEY, R. M. and FERRER, M. I. A consideration of hemodynamic criteria for operability in mitral stenosis and in mitral insufficiency. *Circulation*, 20: 442, 1959.)

patterns which will be presented, we hope that we will be able to select candidates a little more successfully.

As a consequence of this experience at Bellevue, we reviewed our clinical and hemodynamic material, and Dr. Harvey and I believe that there are, roughly, six groups of patients with mitral stenosis that can be identified by a combination of clinical and hemodynamic data. (Fig. 7.)

In the first group (Fig. 7), we present to you the hemodynamics of what is a clean-cut clinical group, in which mechanical mitral block is the predominant feature, with recent and progressive dyspnea as the major symptom. This group has been identified hemodynamically by all the clinics in this country and abroad as showing modest or slightly higher degrees of pulmonary hypertension at rest, and aggravated on exercise. As predicted, this is the group that does well with surgery. The preoperative hypertensive state is relieved.

A second group (Fig. 7), and we have heard of one such from Dr. Wood, probably not only has disturbance of the mitral valve but, in addition, vascular disease of the lungs. This is detected by hemodynamic studies, which show that the pulmonary hypertension is much more severe than in group I and becomes, at times, almost equal to the systemic pressure during exercise. These patients surprised us, as we feared they would not give good operative results because of our estimates regarding the vascular lesions in the lungs. However, we have had a small group of such patients who at the end of five years have shown a distinct fall in pressures and clinical relief of symptoms.

Group III (Fig. 7) is a very interesting one because the patients are only slightly disturbed hemodynamically. They have normal pulmonary artery pressures at rest, as well as a normal response in cardiac output to exercise, but the pulmonary artery pressure rises sharply during exercise. These are the patients whose symptoms, you might say, are just beginning. They are, as Dr. Estes indicated, the patients who, on unusual effort or during pregnancy or some other stressful period, become symptomatic, but do rather well at other times. These we have classified as early or mild mitral block. We have been very pleased with the operative results in such subjects. The response seems to be very good and, usually, as you might predict, the valve is in relatively good condition anatomically.

We now move out of the operative group into those patients with rheumatic heart disease and

mitral stenosis (group IV, Fig. 7) in whom our analysis suggests that the myocardium is largely at fault.

It is immediately apparent to you that, hemodynamically at least, group III, the early block, and this group IV might be similar, at least at rest, but this is not the case clinically. In patients with myocardial insufficiency —and I would like now to speak of them when they are not in overt congestive heart failure— the complaints are quite different, and the findings are too. They complain of fatigue and dyspnea almost all the time. These symptoms become extreme at some moments, and there is limitation of ability to do even minimal work without evidence of congestion. They are usually patients whose hearts are much larger than those of patients with mitral block alone. They very frequently have arrythmias, usually atrial fibrillation, and they give a history of recurrent bouts of congestive heart failure which can be reversed on a medical regimen; hence, although they look like group III hemodynamically, we would tend to group them, if we saw them in a clinic, with the first two groups on the basis of symptoms alone. They are very sick people, as they express this disability to you. In these subjects, as we had suspected would be the case, mitral commissurotomy does not seem to alter the progression of the disease. These same subjects, of course, have episodes of heart failure, and when they are in congestive heart failure (group V) hemodynamically, they might momentarily confuse us because, if you looked only at the pulmonary artery pressures, such patients might seem more like those in groups I and II with mitral block. However, you will find the *clinical* signs of failure in group V in addition to an elevated right ventricular diastolic pressure, the expression of right heart failure which is not unusual in groups I and II. They also have quite a low cardiac output. There are thus many signals in the combined clinical and hemodynamic data of group V to warn us that such a person, when in failure, may not get a good operative result. The clinical evaluation from Dr. Estes' group confirms this.

Of course, the possibility that mitral block could be a factor, perhaps even a predominant one, in these subjects was considered and, for purposes of defining the usefulness of surgery in such cases some of them came to operation in our series. Postoperatively, they were no better off than they had been preoperatively, even though some opening of the mitral valve had been achieved. Evidently, these were patients in whom the myocardium was simply unable to function properly at any level of activity.

Figure 7 summarizes the five groups we have discussed. Those whom we consider not to be ideal candidates for surgery are those in whom there is myocardial insufficiency (groups IV and V), and we have added to these a sixth group (Fig. 7) merely to remind you that there are persons with auscultatory mitral stenosis in whom no significant block exists and who have normal hemodynamics. Naturally, the catheterization procedure is offered to these subjects only if the symptoms are very difficult to evaluate, as may occasionally be the case. It may be hard to tell if the symptoms are of cardiac or other origin.

I am sure you would like to know how the clinical and hemodynamic findings could be grouped in order to select a proper candidate for surgery. There are certain features—and I am sure you will notice immediately that these are in no way different from Dr. Estes' adverse factors—which may indicate that we will get a poor result. Fatigue and weakness are disturbing symptoms. Progressive dyspnea, on the other hand, suggests to us that the surgeon can be of help. The presence of a double mitral lesion (mitral stenosis and mitral insufficiency) indicates the likelihood of poor results. Considerable cardiac enlargement, heavy calcification of the mitral valve, atrial fibrillation, no good evidence of right ventricular enlargement on the electrocardiogram, recurrent bouts of congestive heart failure or intractable failure, all disturb us, as well as the group who, after intensive therapy, have little or no pulmonary hypertension at rest and whose lesion we have called myocardial insufficiency. A good result is likely in patients with symptoms of recent progressive dyspnea, pure mitral stenosis, little cardiomegaly, sinus rhythm, no failure, electrocardiographic evidence of right heart enlargement and moderate to severe pulmonary hypertension at rest. At the moment, these are our criteria, but we cannot, of course, invariably pick the patient who has pulmonary hypertension by clinical means and therefore, in certain patients, as Dr. Estes and Dr. Wood have both said, we have to resort to the physiological data.

DR. LARSON: In summary of this part of the clinic, I think we might say that the natural history of rheumatic heart disease with mitral

valve involvement is changing, due to two causes: (1) the introduction of antistreptococcal prophylaxis, and (2) surgical interference. Furthermore, the incidence of hemodynamically significant disease among those who have once had mitral valvulitis is surprisingly small. There is a new category of "improved" among the group who have become mitral cripples. Perhaps the most distressing feature of our decade of experience with mitral valvulotomy is our inability to identify with certainty those subjects who will be improved by the operation.

It is appropriate at this time to hear a representative from the department which has made this Clinic possible, Dr. McAllister, of the Department of Surgery.

DR. FERDINAND MCALLISTER: I think this sort of appraisal of the problem by non-surgeons is a healthy thing. It tends to keep the surgeons honest. It is too bad that more is not known of the natural history of mitral stenosis. It makes it very difficult for us to appraise the group of patients in whom improvement occurred initially and then symptoms developed which finally put them back again into the category of the unimproved. For example, how do we know how many of these patients would remain in group III* or, if they had not had surgery, might have passed into group IV?* Or how many would have died if not operated on?

It is not always possible from the cold statistical analysis of this problem to form an accurate preoperative appraisal. The ideal candidate has been presented to us, and I agree wholeheartedly that it would seem that such a patient should have a good result. But, unfortunately, the ideal candidate may be a young woman who has a rubbery or leathery type of valve which does not break at the time of surgery and which cannot be easily cut with a knife, so that the amount of opening achieved is submaximal. It has been my experience that there is a high incidence of recurrent difficulties in such patients even though they seem to be ideal candidates. In many instances, therefore, the pathologic anatomy of the valve at the time of surgery is the real determining factor, and this is one thing that we cannot appraise preoperatively.

I would like to say a word about the embolic problem. After reviewing the records of close to 200 cases in this regard, a few interesting features have come to light. There was little difference in the incidence of emboli discharged at operation in the patients who had a previous history of emboli and in those who were fibrillating. In those who had been or were fibrillating at the time of surgery, the incidence of emboli discharged at operation was 15 per cent. Among those who had a past history of emboli, the incidence of emboli discharged at operation was 14 per cent. Thus one of the important features seems to be the presence of atrial fibrillation whether or not emboli have occurred previously, and I personally, in every case of fibrillation, tape the left common carotid and the innominate artery. This has been done for close to five years now, and I have yet to encounter a fatal embolus. Occasionally, it is not wise to try to control the innominate with a tape because of its inaccessibility and we must be satisfied with occlusion of this vessel by external pressure in the neck. But we always control the left common carotid artery at its origin because, in our series, the incidence of cerebral emboli has been three times as great by way of the left common carotid artery as via the right. Furthermore, the disability resulting from an embolus discharged by this route is far greater, because of the loss of speech and righthandedness.

The problem of restenosis disturbs us greatly. As you have seen, our figures for improvement do not seem to compare very well with what you may have read in the literature. I think the reason for this is that this is a long-term follow-up. If one considers the patients who improved originally but who have gotten into trouble later and adds that to the 40 or more per cent who have been improved over the long pull, one approaches the figures reported in the literature for improvement. The long-term evaluation reveals the increasing seriousness of the problem of restenosis.

It seems to me that there are several reasons for the reappearance of difficulty so far as the anatomy of the valve is concerned. One reason for recurring difficulty is extension of rigidity and fixation throughout the valve leaflets. In some patients there has been no refusion at the commissure, but instead the valve has become stiff and rigid throughout its extent, whereas formerly the rigidity involved only the free, flapping edges. This stiff valve acts as a barrier, just as the inflexible valve does in aortic stenosis. A second cause obviously is inadequate commissurotomy, with only a marginal opening, and then restenosis. I have performed a second exploratory operation on patients whose valves

* New York Heart Association classification.

were opened reasonably widely and again found a valve narrowed down to a slit. A third cause for recurrent difficulty is what Dr. Ferrer has pointed out, i.e., the appearance of myocardial insufficiency. Sometimes this has appeared in patients with small left ventricles who could not reasonably have been suspected to have it before operation, because the left ventricle could not be directly tested due to the presence of a tight stenosis. Finally, there is a group of patients who have done well for a considerable period of time and in whom mitral insufficiency developed through the slow progression of distortion of the valve.

We hope that in the future we will be able to replace the mitral valve because it seems to me that this valve, if it is diseased and then damaged again, as it inevitably is at the time of operation, must ultimately develop further scarring, retraction and deformity. I think the hope for the future in mitral disease is direct vision replacement of the mitral valve with an artificial one.

DR. LARSON: Dr. Fishman, would you care to comment on the selection of patients for mitral commissurotomy?

DR. ALFRED P. FISHMAN: Perhaps one or two points may bear emphasis. For want of time, this clinic has not sufficiently emphasized one of the major problems in selecting patients with mitral stenosis for commissurotomy, namely, the hemodynamic significance of associated mitral insufficiency or aortic valvular disease. At the present time, the detection of an enlarged left heart in a patient with mitral stenosis virtually contraindicates mitral commissurotomy. Indeed, the mere recognition of aortic valvular disease in a patient with mitral stenosis usually elicits considerable debate concerning the advisability of commissurotomy because of the prospect that relief of mitral valvular obstruction may exaggerate the hemodynamic significance of the aortic valvular lesion.

The topic of myocardial insufficiency is a particularly cloudy one. On clinical grounds, one suspects that a big flabby heart has a poor myocardium. It is not always easy to predict how this big flabby heart will respond to relief of mitral valvular obstruction. Nor is there any hemodynamic appraisal which will allow one to predict with assurance whether the dilated heart will benefit from commissurotomy. I suspect that while our measurements will probably continue to disclose new hemodynamic patterns, in the last analysis decision for operation will depend on (1) a long-term appraisal of the benefits of surgery as compared to the natural history of mitral stenosis, and (2) clinical evidence that a patient with pure mitral stenosis can no longer be sustained on medical treatment.

DR. RÉJANE M. HARVEY: Since Dr. Fishman raised a question about the use of the term "myocardial insufficiency," we should point out that this is probably not a very elegant term because it is not very definite. It suggests a severely disabled patient with a murmur of mitral stenosis who has an enlarged heart as seen on the roentgenogram. Such patients, when they are rigorously treated for a prolonged period of time on a medical regimen and lose their evidences of congestive heart failure clinically, are found by cardiac catheterization to have normal pressures at rest. These pressures are not changed by exercise and the patients have a fixed and low cardiac output.

As you gathered, we, too, were not certain what to do with these patients in the early years, and operated upon them. We have been sorely troubled because of the fact that we did not improve their clinical course. They continued to have bouts of atrial fibrillation, sometimes uncontrollable, bouts of congestive heart failure, and pulmonary or peripheral emboli.

We still think the disease lies in the heart. I do agree with Dr. Fishman, that there is a spectrum of adult patients with myocardial insufficiency, both clinically and hemodynamically. I think it is of interest that those who have the most successful results from mitral commissurotomy are patients whose congestive failure is of recent origin. The patients who have had a long history of cardiac disability are apt to be the ones with normal pulmonary artery pressures and who do not benefit from surgery.

DR. LARSON: Although we have not yet analyzed the data, we have the same impression as you, that subjects who have been in failure for several years are those who usually end up with poor results. Those whose failure is of recent onset seem to fare much better. Dr. Fishman, what do you believe is the future role of left heart catheterization in attempting to assess these people preoperatively?

DR. FISHMAN: Left heart catheterization is certainly not a prerequisite for surgery in all patients with mitral stenosis. Actually, clinical appraisal, especially by physicians who are familiar with the hemodynamic abnormalities

of mitral stenosis, generally suffices for decision. Progressive dyspnea and fatigue, and progressive diminution of exercise tolerance in a patient who has previously suffered no handicap from mitral stenosis are fairly reliable indices for surgery. In the patient who cannot be trusted to supply an accurate clinical account, right heart catheterization may disclose the functional significance of the murmur.

However, left heart catheterization promises to be necessary in two groups of patients: (1) those with mitral stenosis who may also have mitral insufficiency and/or aortic valvular disease and (2) those suspected of restenosis of the mitral valve after commissurotomy. It must be emphasized that at the present time most laboratories are depending on pressure gradients across the mitral and aortic valves to recognize not only mitral stenosis but also the coexistence of other valvular defects. The hemodynamic significance of these pressure records will be easier to assess when simultaneous measurements of blood flow across the valves of the left heart become feasible.

DR. STANLEY E. BRADLEY: Do these patients with fixed low cardiac output have a marked increase in peripheral venous pressure with exercise?

DR. HARVEY: They often present an elevation in right ventricular end-diastolic pressure, depending on the level of pulmonary hypertension. With a lower degree of pulmonary hypertension, however, you may or may not see a diastolic pressure elevation. We have not measured the peripheral venous pressure.

DR. LARSON: Dr. Richter, would you comment on your experience in relation to the studies presented?

DR. TOR RICHTER: I think that one of the generalizations that can be drawn from this study is that medicine will not hold still while you try to evaluate one procedure. The controls that were available in Bland and Jones's study [*1*] are no longer applicable because of the changes in therapy of rheumatic fever and its complications. There are no control studies for the current group.

The early cases in which Dr. Wood carried out recatheterization consisted of, by and large, the "good risk" patients who had a fairly high operative mortality. The cases that I have seen are, by and large, the complicated ones, so that our experience in a university center may not be typical of the country as a whole. All these things impose difficulties in a statistical analysis of the benefit of mitral commissurotomy.

DR. LARSON: Dr. McAllister, would you say a little more about the possible use of prostheses in the future in repair of the mitral valve?

DR. MCALLISTER: I did mention that I thought the future in this field of surgery lies in replacement with prostheses. We have developed two prostheses here, both of which give us normal pressure tracings in the atrium and left ventricle when implanted, and animals (dogs) in whom this was done have lived for several hours. We are having a great deal of difficulty in getting the animals to live longer. I am certain from the pressure tracings that they are not dying as a result of malfunction of the valve itself, so I have great hopes for these valves. Of course, these prosthetic valves will need extensive testing before we would be willing to implant them. For example, the matter of "fatigue" in plastics—the effective lifespan of a plastic—is given in the industry as of the order of 30 to 40 million stresses. Well, 30 to 40 million stresses would only be a year or two in the lifetime of a patient, and the matter of fatigue in such use of a plastic material has never been explored in industry.

STUDENT: Is there any way of estimating what the nine-year survival would be in comparable groups of unoperated patients?

DR. ESTES: There is no comparable group.

DR. DONALD SMITH: Dr. McAllister, in those patients in whom you found restenosis, either those whose leaflets became much more severely damaged on reoperation or those in whom the valves actually restenosed, what percentage had clinical evidence of a recurrent attack of rheumatic fever?

DR. MCALLISTER: I cannot give you a figure on the percentage. I would say that probably less than a third of them had had overt evidence of recurrent rheumatic activity.

DR. LARSON: I think this is complicated by the difficulty of separating rheumatic activity from the postcommissurotomy syndrome.

DR. EDITH SPROUL: I would like to ask Dr. McAllister if he has any estimate at operation or at autopsy of the state of the chordae tendineae, upon which, after all, the mobility of the valve is so dependent. Can you estimate whether those who failed to respond were those who had tightly fixed and markedly contracted chordae tendineae?

DR. MCALLISTER: If the chordae tendineae

are markedly contracted, it is not uncommon to create a moderate amount of insufficiency on opening the valve. I think there is no question that there has been progressive shortening of the chordae tendineae in some of the valves in which there has been recurrent difficulty. This has contributed to what I mentioned earlier, that is, progressive distortion of the valve.

SUMMARY

DR. NICHOLAS P. CHRISTY: This exercise points out some common misconceptions concerning the natural history of rheumatic heart disease, emphasizing the relative rarity of valvular disease following an attack of acute rheumatic fever, and showing that only a small proportion of patients who have valvular involvement are likely to become ideal candidates for mitral commissurotomy.

An attempt was made to assess the effect of this operative procedure upon the natural history of rheumatic heart disease, an assessment difficult to make in the absence of a truly comparable untreated control group. Of 130 patients subjected to commissurotomy who were followed up for periods as long as eight years after surgery, careful direct clinical study showed improvement in 44 per cent, no change in 21 per cent; 11 per cent were worse and 24 per cent died. The changes in objective findings were less striking than the changes in symptoms. The incidence of hemoptysis was sharply reduced and congestive heart failure and dyspnea were improved in over half the patients; on the other hand, murmurs and cardiac size tended either to remain the same or to change in an adverse direction. Operative deaths were chiefly caused by emboli, congestive heart failure and bacterial endocarditis. The operative outcome seemed to be adversely affected by the preexistence of severe, long-standing heart failure, calcification of the mitral valve, and a cardiac classification of IV. All observers believed that present criteria for selection of patients for commissurotomy are far from perfect, but the participants agreed that youth, a small heart in regular sinus rhythm, and recent deterioration predisposed to a good operative result.

Objective observations of the effect of the operation upon the natural history of rheumatic heart disease are recorded. Right heart catheterization showed early physiologic improvement following commissurotomy, and demonstrated that such improvement could be sustained for years. The value of left heart catheterization in selected patients (those with associated mitral insufficiency or aortic valvular disease, patients suspected of restenosis of the valve after commissurotomy) was indicated as a measure of the degree of mitral block. It was suggested that the spectrum of patients with rheumatic heart disease can be roughly arranged in groups in terms of myocardial versus mechanical (mitral block) lesions, a classification which may lend further aid in evaluating the suitability of patients for operation.

The surgical problem was discussed in relation to the mechanical changes that may conduce to restenosis of the valve after operation, e.g., increasing stiffness of the valve itself, and shortening and fixation of the chordae tendineae. It is hoped that the insertion of prosthetic mitral valves may offer hope for the future.

The somewhat pessimistic operative results here recorded are at variance with certain earlier, more enthusiastic reports. The discrepancies depend upon several factors: duration and objectivity of medical follow-up; additional changes in the natural history of rheumatic fever superimposed by other therapy, especially prophylaxis; and differences of opinion about what is the true natural history of this disorder. Certainly the natural history is changing, and mitral commissurotomy, in a very small group of the total number of rheumatic subjects, appears to be contributing to the change.

Acknowledgment: We are grateful to Dr. Alfred P. Fishman for his generous help and advice, especially with regard to the physiologic studies, which were carried out in the Cardio-Pulmonary Laboratory of the Presbyterian Hospital.

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Clinicopathologic Conference

Acute Renal Failure of Obscure Etiology

STENOGRAPHIC REPORTS, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A FIFTY-EIGHT year old white man was admitted to the Genitourinary Service with the chief complaint of uremic poisoning.

The patient had complained of low back pain two months prior to admission. This was thought to be related to trauma. Otherwise he had been in good health. Ten days prior to admission his urine output decreased. During this ten day period he had oliguria and hematuria. Progressive weakness developed and he appeared ill to his wife. During the three days prior to admission the patient vomited several times and complained of abdominal bloating. There had been no symptoms of nocturia, frequency, dribbling or hesitancy. The patient was catheterized at another hospital and started on a regimen of Furadantin.® He was then transferred to Barnes Hospital with a reported nonprotein nitrogen of 111 mg. per cent. The past history was non-contributory except for an appendectomy.

On physical examination the temperature was 37°c., pulse 80, blood pressure 180/90 mm. Hg and respirations 22/minute. The patient was a well developed, obese, white man, lying in bed, breathing deeply and rapidly. Skin was of good turgor. Chest was clear with increased anteroposterior diameter. The neck veins were full. The rest of the physical examination was within normal limits.

The laboratory data were as follows: Hemoglobin 11.4 gm. per cent, white blood cell count 7,100 per cu. mm. with a differential of 78 per cent segmented forms, 18 per cent lymphocytes, 4 per cent monocytes. Urinalysis showed a specific gravity of 1.012; 4-plus protein and many red blood cells with 15 to 20 white blood cells. The serum sodium was 137 mEq./L., serum potassium 9.9 mEq./L., alkaline phosphatase 4.4 Bodansky units, acid phosphatase 1.8 units, total protein 7.5 gm. per cent with albumin 3.4 gm. per cent and globulin 4.1 gm. per cent. The blood urea nitrogen was 104 mg. per cent; creatinine 19.1 mg. per cent, calcium 9.8 mg. per cent, phosphorus 14.6 mg. per cent, chloride 104 mEq./L., and carbon dioxide 11.9 mEq./L.

Roentgenograms of the abdomen and a left retrograde pyelogram showed bilateral enlargement of the kidneys and normal left renal calyces, pelvis and ureter. Two electrocardiograms were both read as nodal tachycardia with prolonged QRS or slow ventricular tachycardia, compatible with hyperkalemia.

A venous pressure obtained immediately after admission was 330 mm. saline. The patient underwent a cystoscopic examination and catheters were introduced into both ureteral orifices. There was no evidence of obstruction. During the night the patient became more short of breath and the nasal administration of oxygen was started. On the morning of the day he died, the patient was found to be in extreme respiratory distress, breathing at a rate of 60/minute. He was sitting propped up in bed and was cyanotic. The pulse was 104, the systolic pressure was 100 mm. Hg by palpation. The neck veins were engorged and the chest was clear. Intravenous fluids, containing 20 per cent glucose, heparin, calcium gluconate and insulin, were administered. A potassium binding resin was given rectally at the same time. A deeper coma developed and the patient died about two and a half hours later.

CLINICAL DISCUSSION

DR. SOL SHERRY: Todays case is one of renal failure of obscure etiology. Two problems are posed: (1) the cause of renal failure and (2) the immediate cause of death. Unfortunately, the patient was not under observation long enough to obtain an adequate workup. All we can hope

for is a fairly reasonable guess. Dr. McAlister will discuss the roentgenographic findings.

DR. WILLIAM MCALISTER: We had a total of three roentgenograms on this patient. The first was a plain roentgenogram of the abdomen; the second was a film with bilateral ureteral catheters in place; and the third had contrast material injected in the left kidney. The spine revealed some degenerative changes. The psoas shadows were seen bilaterally. The over-all renal outlines appeared somewhat enlarged, with the left being a little larger than the right. On the left retrograde pyelogram the calyces and pelvis appeared normal; there was no evidence of distortion of the collecting system and certainly no evidence of obstruction.

DR. SHERRY: Were any bone lesions present?

DR. MCALISTER: Not that I could see. The pedicles and what I could see of the vertebral bodies and pelvis appeared normal. There was no evidence of vascular calcification.

DR. SHERRY: In your estimation, were both kidneys enlarged?

DR. MCALISTER: Yes.

DR. SHERRY: One of the possibilities, which we shall have to consider, is bilateral renal vein thrombosis. Were the roentgenographic findings compatible with such a diagnosis?

DR. MCALISTER: Well, the enlargement would be, but the normal collecting system would be against it; experimentally, by producing occlusion of the renal vein, the kidney will increase two to three times the normal size. The kidney in retrograde pyelography will have an appearance not unlike that of a polycystic kidney. There was no evidence of calyceal distortion in this case. I think the normal collecting system would be a strong point against renal vein thrombosis.

DR. SHERRY: Dr. Massie, would you discuss the electrocardiographic findings?

DR. EDWARD MASSIE: Let us first consider the effect of increasing levels of potassium on the electrocardiogram. As the potassium rises to 8 mEq./L., the T wave becomes tall and peaked, especially in the V leads. The U wave is usually absent and then as the potassium level continues to rise there follows a diminution in the amplitude of the R wave and later the P waves may disappear (auricular arrest). At higher levels, the QRS complex becomes widened with depression and even obliteration of the S-T segment. With the potassium level in the range of 10 mEq./L. the QRS is so prolonged that it blends with the elevated T wave to produce a diphasic curve. Now let us discuss the electrocardiograms of this patient. Remember that the patient had a potassium level of 9.9 mEq./L. In these tracings the presence of the biphasic QRS complex, and the absence of the P waves, were totally in keeping with severe hyperkalemia.

DR. SHERRY: Since the patient had a serum potassium of almost 10 mEq./L., and the electrocardiographic findings were so impressive for a hyperkalemic effect, let us consider whether or not the patient died of potassium intoxication. Dr. Smith, how does hyperkalemia affect the myocardium other than through changes in impulse conduction? I say this because the patient did not demonstrate bradycardia or arrhythmia, but a rapidly rising venous pressure, increasing dyspnea, tachypnea and a falling blood pressure. These latter findings suggest an acutely failing myocardium.

DR. JOHN R. SMITH: It is very well known that, when the potassium level of the serum rises above 7 or 8 mEq./L., serious defects in membrane potential fluctuation may occur, and conduction of cardiac impulse as well as the operation of pacemakers may be affected. The heart can be brought to standstill and held in complete abeyance simply by flooding it with a high concentration of potassium. It is possible that some of the cardiac manifestations in this case were directly referable to potassium intoxication. As extracellular potassium concentration increases, contraction eventually decreases. The exact mechanism by which this is brought about in the myocardial cells is obscure. Enzyme liberation and energy production and utilization by the myocardium may be involved. Under the conditions that existed here, there was auricular arrest, and the heart was made to go upon a pacemaker which fortunately arose somewhere around the auricular-ventricular area or at the base of one of the ventricles. There was probably a very serious diminution of myocardial power, the exact opposite of a digitalis effect. The severe rise of venous pressure and the other manifestations of congestive heart failure may have resulted from curtailment of myocardial function compromised by potassium intoxication.

DR. SHERRY: Is it not true that in severe hyperkalemia, the heart may arrest in diastole and with considerable engorgement?

DR. SMITH: That is true, and the power of contraction or the power of systole is often diminished before cessation of heartbeat occurs.

DR. SHERRY: I have searched through reports on patients who have died with potassium intoxication; most of these comment on the development of arrhythmias, other bizarre findings, and the development of asystole at very high potassium levels. Although very little comment is made of acute heart failure, when reading through these descriptions one is impressed that not infrequently the patient with severe hyperkalemia suddenly has an acute heart failure with hypotension and engorgement of the circulation. Therefore, I wondered whether, in our patient, the potassium intoxication was expressing itself primarily as a failure of myocardial contractility with rapid cardiac enlargement and circulatory engorgement.

DR. SMITH: That, I think, is quite correct. It is certainly the best explanation for the symptomatology and the train of events that were observed.

DR. SHERRY: Dr. Parker, would you agree with this interpretation?

DR. BRENT M. PARKER: I was able to find several references to cardiac failure in terminal hyperkalemia. I think this is a very reasonable explanation. The one thing that bothers me about this is that the chest was described as being clear. I do not know who listened or how carefully, but if this were the case, and he was dyspneic from congestive failure, one would have expected that he would have had râles.

DR. SHERRY: Dr. Massie, do you accept our interpretation of potassium intoxication as the cause of the patient's myocardial failure?

DR. MASSIE: Yes, this seems to be a logical deduction.

DR. SHERRY: We have fair agreement then as to the cause of death; we can turn now to the nature of the renal problem. It would simplify matters considerably if we were reasonably certain that we were more concerned with a problem in acute renal failure rather than chronic renal disease. Dr. Morrin, do you think we are justified in believing our patient's problem was one of relatively acute renal failure?

DR. PETER A. F. MORRIN: I would agree that everything here points to acute renal failure, although we cannot rule out the possibility of some underlying chronic disease. The story is incompatible with chronic renal failure for the following reasons: There was no history pointing to chronic renal disease, and there was no mention of any polyuria or nocturia which are well known characteristics of chronic renal insufficiency. Apparently the patient was obese, and many of these patients with chronic uremia have significant weight loss. There was no mention of any pigmentation of the skin, which is frequently seen, and his anemia was not very severe. Finally, his kidneys were described as being large. This is certainly very strong evidence against chronic Bright's disease. Chronic renal failure can occur with large kidneys, however, in certain instances. These include lupus erythematosus, myeloma, and possibly Kimmelstiel-Wilson's disease.

DR. SHERRY: One other point, which I would use in favor of acute renal failure, is the very high potassium level in the presence of only a moderate elevation in the blood urea nitrogen level. In my experience, patients with chronic renal failure usually show the reverse; that is, high blood urea nitrogen levels with low, normal or only moderately elevated serum potassium levels. Is this agreeable to you, or would you take issue with this point?

DR. MORRIN: I think this is generally true, Dr. Sherry, but the rise in potassium depends on so many factors, such as the potassium intake, the rate at which tissues are breaking down, the severity of the renal failure, and the degree of compensation in the remaining functioning nephrons. I would not like to place too much emphasis on this point.

DR. SHERRY: Of course, it is intriguing to consider the mechanisms responsible for this dissociation between the rise in urea nitrogen and the potassium level. However, in our patient it would serve no purpose, since he was at home most of this time and we know nothing about his potassium intake; for all we know he may have been drinking orange juice all the time.

Dr. Perry, do you believe that this is a problem in acute renal failure?

DR. MITCHELL PERRY: This seems to me to be the most likely possibility, for the reasons that Dr. Morrin cited.

DR. SHERRY: Dr. Nickel, would you agree as well?

DR. JAMES F. NICKEL: Yes, I think Dr. Morrin's points are well made, with one possible exception. I am disturbed about the serum calcium level, which remained normal despite a marked elevation of the serum phosphorus. We ordinarily would expect, even with acute renal failure, to find the serum calcium level below normal. This would seem to me to be a bit unusual. Otherwise, everything seems compatible with acute renal failure.

DR. SHERRY: On admission to the hospital the urological service ruled out the possibility of an obstructive lesion. On clinical grounds it also seems reasonable to eliminate the other more common causes of acute renal failure, such as acute tubular necrosis, necrotizing papillitis and bilateral cortical necrosis, other than the type occasionally seen with bilateral acute arterial obstruction. After eliminating these, five possibilities remain for serious consideration: acute glomerulonephritis; some type of necrotizing angiitis, that is, some variant of polyarteritis; bilateral renal arterial disease such as thrombosis, embolism or perhaps dissection; bilateral renal vein thrombosis; and some infiltrative or intrarenal obstructive disease masquerading as acute renal failure, an example of which would be myeloma. The presence of a normal serum calcium level despite a high concentration of serum phosphorus could support the latter as a possibility.

Dr. Gedney, do the urinary findings in this patient give us any clue as to the type or types of lesions we should consider most strongly?

DR. W. BURTON GEDNEY: The urinary findings in this case were very scant, and I do not think that any definite conclusions can be drawn from the information that we have. However, we cannot rule out acute glomerulonephritis. We would like to see some blood casts or have some other information of a more detailed nature on the urine before any conclusions could be drawn. I do not think that the urinary sediment in this case is diagnostic.

DR. SHERRY: If it were true that red blood cell casts were absent from the urine, do you believe that we could eliminate acute glomerulonephritis?

DR. GEDNEY: I do not think that you can definitely eliminate it, but we would like to see some casts in the sediment to make the diagnosis. However, at times it requires a very detailed examination of the urinary sediment to turn up the blood casts; apparently this either was not done or at least was not reported.

DR. SHERRY: Let me now ask the question in reverse. Supposing one could substantiate that red cell casts were present; what diagnostic considerations would this favor? Certainly, acute glomerulonephritis would be one.

DR. GEDNEY: I think that acute glomerulonephritis would be one, necrotizing angiitis another. Bilateral renal arterial disease, as you have listed, is not. It can be associated with casts, although most of the time in acute arterial occlusion a paucity of findings are found in the urinary sediment.

DR. SHERRY: Then the presence of red blood cell casts would strongly favor the presence of an acute glomerulitis, regardless of etiology. Dr. Daughaday, do you believe there are any clues in the serum electrolytes or blood chemistries concerning the nature of the renal lesion?

DR. WILLIAM H. DAUGHADAY: No, I think the changes were those of a virtually complete cessation of urine formation. The problem of the serum calcium has already been discussed. I think I would agree with Dr. Nickel that this one bit of evidence would suggest a more chronic renal insufficiency in which there had been adequate time for secondary hyperparathyroidism to occur.

DR. SHERRY: Dr. Morrin, do you agree with the differential diagnosis previously presented?

DR. MORRIN: Yes.

DR. SHERRY: What is your impression as to the most likely diagnosis in this case?

DR. MORRIN: I think from a purely statistical point of view, we have to consider acute glomerulonephritis as being the most likely cause of the sudden development of anuria and hematuria in this man. It is commonly believed that glomerulonephritis is a disease of the younger age group, but this concept has to be modified. A recent study from the Boston City hospital,* which admittedly has an elderly patient population, found that the mean age of death from acute glomerulonephritis was about fifty-six years, with the oldest patient being over eighty. We can, therefore, by no means rule out glomerulonephritis on the basis of age.

DR. SHERRY: Is it not also true that acute glomerulonephritis in the older age group has a much worse prognosis than in the younger age group, is quite variable in its clinical pattern, and often atypical?

DR. MORRIN: This appears to be so, Dr. Sherry. It is certainly our impression and the impression of most clinicians.

DR. SHERRY: Of course, against the diagnosis of acute glomerulonephritis, which statistically may still seem the most attractive, is the fact that the hematuria albuminuria, and renal failure occurred in the absence of hypertension, edema or a history of a recent infection.

DR. MORRIN: I would list hypersensitivity

* HESION, H. R. and ROBBINS, S. L. Glomerulonephritis in older age groups. *Arch. Int. Med.*, 105: 23, 1960.

angiitis, of the type described by Knowles and co-workers,* next. These authors reported ten cases of a series of forty-five cases of necrotizing angiitis. Hypertension was not present in any of their cases. The course was very acute, terminating in death within two weeks in nine of the ten; seven cases were attributed to sulfonamide sensitivity. In this patient we have no history of an etiologic factor. Nevertheless, I think we must give necrotizing angiitis definite consideration in our differential diagnosis.

DR. SHERRY: But is it not also true that the patients to whom you refer had symptoms and signs suggestive of other organ involvement, and that all of these patients were febrile throughout their illness? Our patient was supposedly afebrile throughout his entire illness.

DR. MORRIN: Yes, and this makes hypersensitivity angiitis less probable. The next possibility on your list is bilateral renal arterial disease. If this condition were present it would have had to involve both kidneys and all the nephrons in each kidney. We can postulate bilateral renal arterial emboli, but without an apparent source and without evidence of emboli elsewhere, we are on insecure ground in making this diagnosis. I, like you, considered the possibility of aortic dissection. However, in the great majority of these cases the patients have far more back pain than this man manifested; frequently in cases of dissection one or another renal artery tends to be spared to a certain extent.

DR. SHERRY: Furthermore, there was no evidence on the abdominal films or physical examination to suggest a local vascular lesion.

DR. MORRIN: Your next consideration was bilateral renal vein thrombosis. The roentgenogram of the normal collecting system tends to militate against this. We have no underlying cause, and most cases of bilateral renal vein thrombosis have been associated either with some underlying disease, such as renal amyloidosis or thrombosis elsewhere in the body, neither of which were present. However, it has been reported to occur in apparently healthy persons and could give us the clinical and urinary findings that we found in this man.

DR. SHERRY: Yes, bilateral renal vein thrombosis could account for a good part of the picture. However, as you mentioned, this is not the type of case in which we usually find a renal vein thrombosis. Such persons either have an ascending thrombophlebitis, in which case there is evidence of inferior vena caval obstruction, or they have severe infection as the inciting cause. But it is also possible that some other underlying renal disease may be complicated by renal vein thrombosis.

DR. MORRIN: In relation to ascending infection, in many cases of renal vein thrombosis which have been described, the thrombosis apparently started in the smaller vessels of the kidney and extended into the major renal veins and vena cava. At autopsy the clots in the renal veins were more recent histologically than the ones in the smaller venous radicles.

DR. SHERRY: This is certainly true in renal amyloidosis which has a significant association with renal vein thrombosis. Under this circumstance, the thrombi form in small vessels and then spread.

DR. MORRIN: With respect to infiltrative diseases, we must mention amyloidosis. However, we have no evidence for secondary amyloid, and primary amyloid is a rare disease which does not typically involve the kidneys; however I see no good evidence for this diagnosis. Myeloma is a definite possibility in view of the history of back pain followed by rapidly developing renal failure in the presence of large kidneys. The association of myeloma and large kidneys is well recognized, but against this diagnosis is the fact that the patient had severe hematuria, which is not characteristically found with the myeloma kidney. Also, renal failure apparently developed with unusual rapidity. Nevertheless, myeloma kidney remains a definite possibility and would help to explain the abnormal serum calcium.

DR. SHERRY: The elevated serum globulin level is also a point in favor of myeloma. As you noted, myeloma is not a statistically attractive diagnosis, but it is an intriguing possibility in a person with back pain, large kidneys, hyperglobulinemia and a calcium level well out of proportion to the high serum phosphorus concentration. Furthermore, renal failure is the second most common cause of death in myeloma. The presence of hematuria is a little against the diagnosis of a myeloma kidney since gross hematuria has not been described in the usual form of renal failure associated with myeloma. But, in the protocols on patients dying with myeloma kidneys, hematuria is not an unusual finding, although not a prominent manifesta-

* KNOWLES, H. C., JR., ZEEK, P. M. and BLANKENHORN, M. A. Studies on necrotizing angiitis. *Arch. Int. Med.*, 92: 789, 1953.

tion. Before the conference Dr. Carl Moore suggested that hematuria could be explained in a patient with myeloma kidney as a result of uric acid deposits.

It is also of interest that acute renal failure can occur in myeloma following intravenous pyelography; five instances of acute renal failure following this procedure are reported in the literature. Although the mechanism for the failure is not completely understood, it is suspected that dehydration may contribute to the sudden failure.

Dr. Perry, which of the various diagnoses considered here seems most attractive to you?

DR. PERRY: The lack of history limits us severely. Of the diagnoses listed, the last one seems most attractive statistically. I do not know that I can go very much further than that.

DR. MASSIE: Should a toxic agent be considered?

DR. SHERRY: There was nothing in this patient's history to suggest that he had received any toxic agent or any therapy of any kind prior to the onset of his oliguria and hematuria. The first agent given was Furadantin®; he received this three days before admission when his disease was well advanced.

Dr. Nickel, what do you believe is the cause of the renal failure in this patient?

DR. NICKEL: Well, I would agree that it probably makes sense to consider acute glomerulonephritis most seriously. However, I am disturbed by the specific gravity of 1.012 in a man who was oliguric. The urinary output was approximately only 100 cc. per day. I think we would have expected a higher urinary specific gravity this early in the usual course of acute glomerulonephritis. Taking all the things combined that have already been mentioned: relatively high calcium, hyperglobulinemia, back pain proteinuria and renal insufficiency, I would be willing to think most seriously about multiple myeloma.

DR. SHERRY: Dr. Moore, have you ever seen acute renal failure occur in myeloma?

DR. CARL V. MOORE: Not with this rapid an over-all clinical course. Furthermore, all the patients I have seen in whom renal failure developed as a result of myeloma have had definite evidence of that disease at the time. Here we can do little more than engage in a guessing game; we do not have the data to say anything more than you have already said.

DR. SHERRY: We may offer as our final diagnosis that the patient died of potassium intoxication, secondary to renal failure of obscure etiology. Statistically, we believe that an acute glomerulonephritis probably will be demonstrated, but we are certainly intrigued by the possibility of myeloma kidneys masquerading as acute renal failure.

PATHOLOGIC DISCUSSION

DR. GEORGE D. SORENSON: At autopsy the patient appeared well developed and obese. The heart weighed 470 gm. but it was not dilated. There was very slight coronary arteriosclerosis and histologic examination revealed resultant slight myocardial fibrosis. The peripheral portions of the lungs contained scattered small calcified nodules and there was some chronic granulomatous inflammation of the hilar lymph nodes. The etiology of the remote inflammation in these two sites was not definitely established. Slight pulmonary congestion was also present.

The liver weighed 2,200 gm. and microscopically contained fatty metamorphosis which was mainly in the portal areas. There was also moderate, focal hematopoiesis in the liver. (Fig. 1.) The spleen weighed 400 gm. and was very soft on gross examination. Microscopically, it also contained some small areas of hematopoiesis.

The bones were normal on gross examination. However, on microscopic examination the marrow of the ribs, sternum and vertebrae was extremely hypercellular. (Fig. 2.) In a few places some of the residual fat remained but this was largely obliterated. Occasional megakarocytes could be recognized but almost all of the other cells within the marrow cavity were plasma cells and this was considered diagnostic of multiple myeloma. (Fig. 3.)

The kidneys were enlarged, each weighed approximately 300 gm. The cut surface bulged and was evidently swollen. The cortex was widened but the cortical-medullary junction was clearly distinguished. There was mucosal hemorrhage in the left renal pelvis along with three small grey calculi and some clotted blood.

In patients with multiple myeloma the kidneys may be affected in at least three ways: first by the development of renal amyloidosis; second by a direct infiltration of plasma cells; and third by the development of renal tubular casts with degeneration of tubular epithelium. In this patient, it was the latter type of disease.

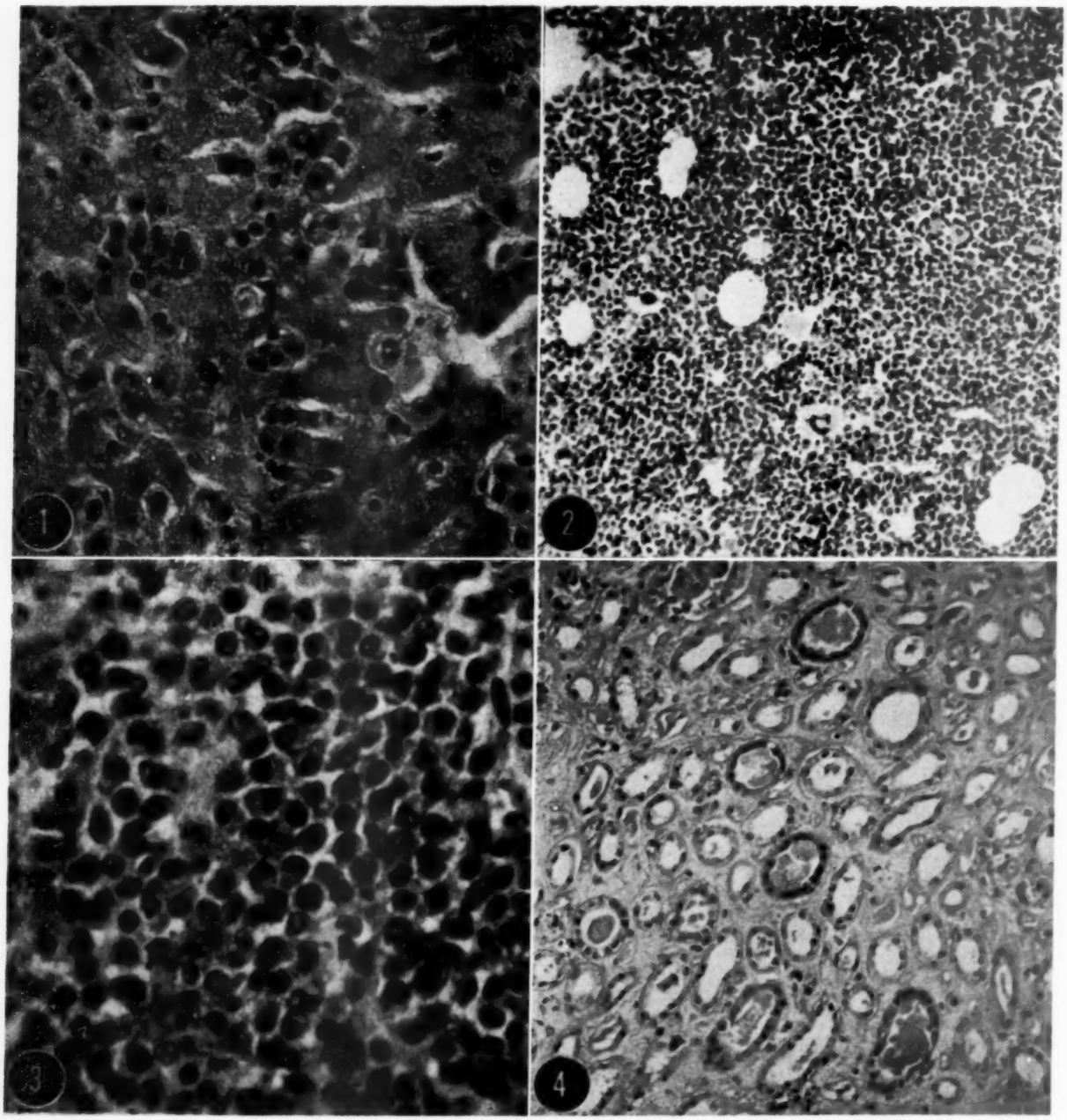

FIG. 1. A portion of liver with islands of hematopoietic cells among the hepatic cords. Hematoxylin and eosin, magnification × 350.

FIG. 2. Hypercellular vertebral bone marrow with a small amount of residual fat. Hematoxylin and eosin, magnification × 150.

FIG. 3. The normal hematopoietic elements of the vertebral bone marrow are almost entirely replaced by the myeloma plasma cells. Hematoxylin and eosin, magnification × 600.

FIG. 4. A portion of the renal medulla illustrating the numerous casts within the tubules. Hematoxylin and eosin, magnification × 150.

The glomeruli were essentially normal and the main abnormalities were in the tubules. Many of the renal tubules contained eosinophilic casts which often filled the lumens. (Fig. 4.) When the tubules happened to be sectioned in a longitudinal direction the cast extended for long distances within the tubules. The tubular epithelium showed degeneration or flattening and

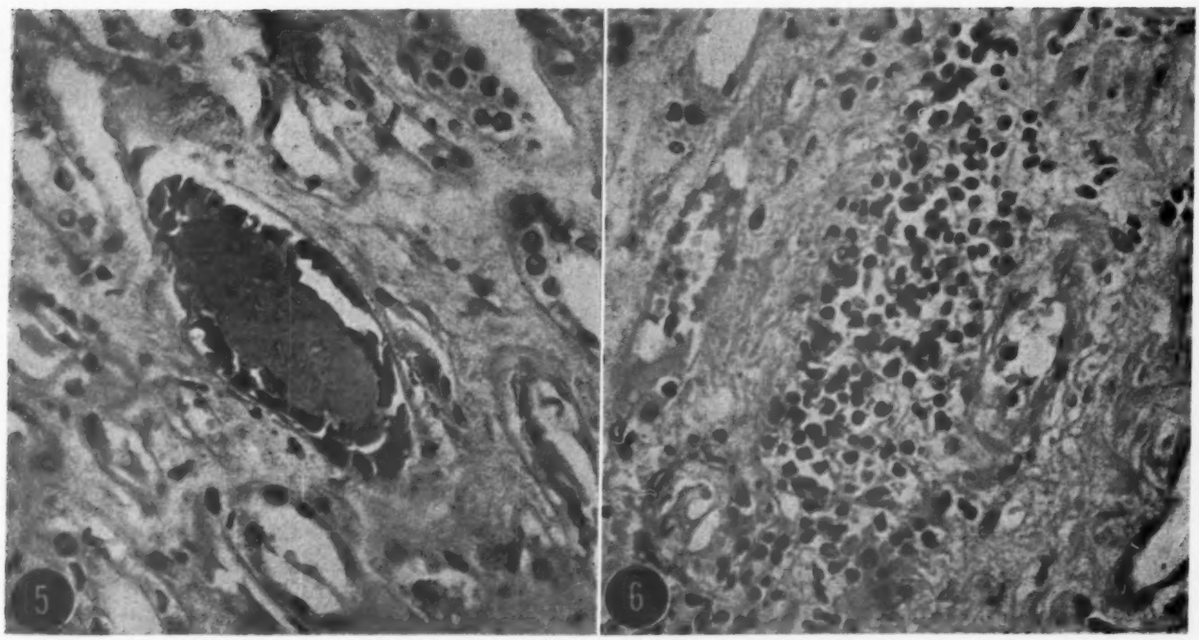

FIG. 5. An eosinophilic cast filling the lumen of a renal tubule. There is degeneration of the tubular epithelium about the cast. Hematoxylin and eosin, magnification × 350.

FIG. 6. A focus of acute inflammation within the renal medulla. Hematoxylin and eosin, magnification × 350.

focal necrosis. (Fig. 5.) In a few places giant cell formation was observed.

In addition to the myeloma nephropathy there was a pyelonephritis with focal accumulations of acute inflammatory cells within the kidneys. The inflammation was most evident in the renal medulla. (Fig. 6.) Permission was not granted for examination of the brain.

Renal failure is not an uncommon occurrence in patients with multiple myeloma. However, usually renal function deteriorates late in the course of the disease and only rarely does acute renal failure occur as a very early manifestation.

The primary anatomical diagnoses are as follows: multiple myeloma, diffusely involving ribs, sternum and vertebra; myeloma nephropathy, advanced with tubular rhexis, tubular necrosis and casts; renal stones in pelvis of the right kidney (two); acute focal pyelonephritis; hemorrhage into renal pelvis of the right kidney; extramedullary hematopoiesis in the liver, advanced, and spleen; acute congestion of lungs, liver and spleen, slight; arteriosclerosis of aorta and coronary arteries, slight; focal fibrosis of myocardium; small calcified pleural and subpleural nodules on the lungs; remote granulomatous inflammation of hilar lymph nodes; focal fatty metamorphosis of the liver.

DISCUSSION

DR. SHERRY: Dr. Sorenson, what was the nature of the calculi that were found in the renal pelvis? Was their composition determined?

DR. SORENSON: I have no information on those, other than they were small.

DR. MORRIN: Was there any evidence of renal vein thrombosis?

DR. SORENSON: No, there was not. The larger and smaller vessels were clear.

DR. MOORE: Would uric acid crystals in the tubules be preserved by the ordinary method of fixing tissues, or would frozen sections be necessary?

DR. SORENSON: If there are very large deposits we can see them on hematoxylin and eosin stains. However, if you want to study them, critically frozen sections and alcohol fixation are necessary.

Case Reports

The Changing Pattern of Circulating Iodinated Amino Acids in a Case of Thyrotoxicosis*

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THE nature of the defects responsible for the association of hyperplastic goiters and hypothyroidism has in part been elucidated by radiochromatographic analyses of circulating iodinated amino acids or proteins [*1*]. The application of these technics to the study of euthyroid patients with goiter has not for the most part demonstrated any abnormalities. The circulating amino acids of goitrous euthyroid patients are in most instances the same as those found in euthyroid non-goitrous people, namely T_4 (thyroxine) and T_3 (triiodothyronine). However, in some cases of goiter in euthyroid patients, a butanol-insoluble iodinated compound has been found [*2*], and the occurrence of hyperfunctioning goiters in euthyroid patients as a result of thyroidal enzymatic defects has been demonstrated by our observation of an euthyroid goitrous patient whose circulating thyroid compound was chiefly T_3 [*3*]. During a continuing study of patients with goiter by use of radiochromatography we observed another euthyroid patient who produced only T_3, and a thyrotoxic patient whose major circulating iodinated amino acid was T_3. We thought it of interest to report on this latter patient because of the occurrence of thyrotoxicosis in a patient with an abnormal pattern of circulating thyroid substances, and because the radiochromatographic pattern reverted following the use of T_3 to that usually seen in thyrotoxic patients.

CASE REPORT

R. K., a nineteen year old girl, was seen in the Endocrine Clinic, Jefferson Medical College Hospital with the complaints of weight loss, nervousness, tremor, palpitations and dyspnea of one year's duration. Examination revealed a weight of 100 pounds, pulse rate of 140 and blood pressure of 130/56 mm. Hg. Except for stare there were no eye signs. The thyroid gland was diffusely enlarged. The skin was warm and moist and tremor of the tongue and fingers was present. The basal metabolic rate was plus 21, the circulation time was eight seconds (Decholin,® arm to tongue). The protein-bound iodine was 6.5 μg. per cent, on one occasion and 6.5 μg. per cent on another. The twenty-four hour uptake of I^{131} by the thyroid gland was 42 per cent, the conversion ratio was 60 per cent. Radiochromatograms of unextracted plasma and the n-butanol extracts of plasma twenty-four hours following the ingestion of 250 μc. of I^{131} were developed in the butanol-ammonia-ethanol system, the acetic acid-water system and the butanol-tertiary amyl alcohol system. In each system used the major areas of activity corresponded to the stable markers for iodide and T_3, with only traces of activity at T_4. (Fig. 1.) Chromatograms of the urine in these same systems showed activity only at iodide.

For the next six months the patient was given triiodothyronine, 125 μg. daily. During this period she was less nervous, the pulse rate was 90 and she gained 10 pounds in weight. The studies were repeated while she was still taking triiodothyronine medication. The protein-bound iodine was 5.6 μg. per cent, the twenty-four hour uptake of I^{131} by the thyroid gland was 62 per cent, the conversion ratio was 95 per cent. Radiochromatograms showed that the activity was now concentrated at the iodide and T_4 spots. (Fig. 2.) Treatment with triiodothyronine was discontinued. Subsequently she remained well, married and became pregnant. The pregnancy was uneventful and the delivery of a normal child was uncomplicated. One month prior to delivery the protein-bound iodine was 8.2 μg. per cent.

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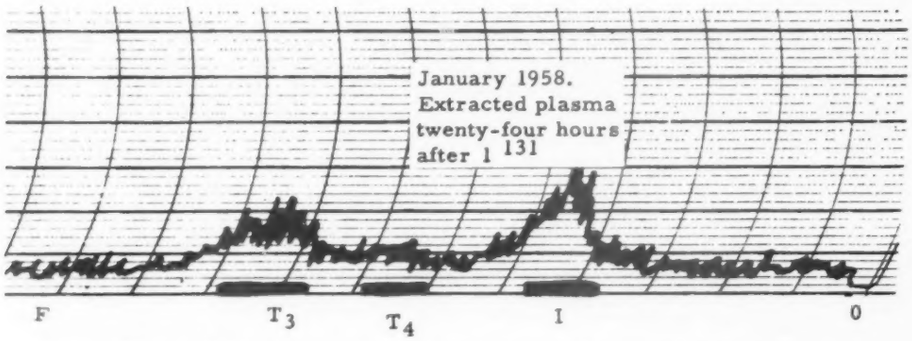

FIG. 1. Radiochromatogram, butanol-ethanol ammonia system.

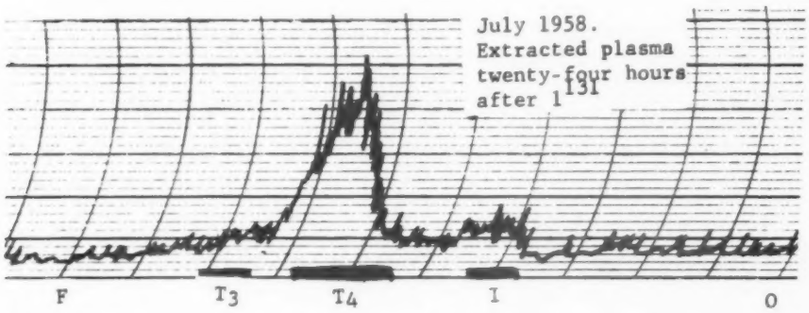

FIG. 2. Radiochromatogram, butanol-ethanol-ammonia system while using T_3.

COMMENTS

The pattern of the circulating iodinated amino acids initially found in our patient differs from that usually seen in patients with thyrotoxicosis. In our case the major circulating iodinated amino acid was T_3, with negligible amounts of T_4, whereas the usual finding in thyrotoxicosis is that of T_4, with only small amounts of T_3 [*4*]. This finding at the time of the initial study seemed to explain the occurrence of thyrotoxicosis in a patient with normal levels of protein-bound iodine inasmuch as T_3 is more potent than T_4. The observation furthermore showed that thyrotoxicosis could occur in a patient with an enzymatic defect of thyroidal hormone synthesis.

Treatment with triiodothyronine was started in order to determine whether the uptake of I^{131} by the thyroid gland could be suppressed by ingesting substances with thyroid activity. This procedure causes depression of uptake in euthyroid but not in thyrotoxic patients [*5*].

The treatment was continued for six months at which time the protein-bound iodine was unchanged, and the I^{131} uptake by the thyroid gland was, if anything, higher than it had been prior to the use of triiodothyronine. In this respect the response was typical of thyrotoxicosis. However, after six months of treatment with T_3 the patient showed marked clinical improvement.

The radiochromatographic pattern of circulating iodinated amino acids at this time showed disappearance of the abnormality originally found in this case, the pattern having reverted to that found in typical cases of thyrotoxicosis. Instead of T_3 being the predominant circulating compound, T_4 was now mainly present, with only small and insignificant amounts of T_3. The cause for this change in the circulating iodinated amino acids is not apparent. It coincided with the period of treatment with T_3, but whether the latter was responsible for the change in pattern cannot be stated. If the almost exclusive secretion of T_3 rather than T_4 in this case, and in an euthyroid goitrous patient reported on previously [*3*], is the result of abnormal synthesis, possibly due to an enzyme defect in the thyroid gland, it is remarkable that this abnormality of synthesis is not fixed, but reversible, either spontaneously or brought about in some unknown way by treatment with T_3. No such complete reversal of abnormalities of thyroid hormone synthesis has heretofore been observed.

The partial remission of the thyrotoxicosis

incident to treatment with T_3 is difficult to explain unless it is to be considered a spontaneous remission, unrelated to treatment. The observation is reminiscent of the equally unexplained remissions reported by Rienhoff in thyrotoxicosis treated preoperatively with desiccated thyroid [*6*].

SUMMARY

A case study is presented of a patient with thyrotoxicosis whose major circulating iodinated amino acid was T_3, presumably as the result of an enzymatic defect of thyroidal hormone synthesis. Treatment with triiodothyronine was associated with partial clinical remission. Neither the protein-bound iodine nor the thyroidal uptake of I^{131} was altered by treatment but the radiochromatograms indicated that the pattern of the circulating iodinated amino acids reverted to that usually found in patients with thyrotoxicosis.

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Reversal of Diurnal Rhythm in Excretion of Water and Salt in Primary Hyperaldosteronism*

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NOCTURNAL polyuria occurring in patients with primary hyperaldosteronism has been attributed to a defect in renal concentrating ability coupled with a poorly defined disturbance of the diurnal rhythm of urine formation [*1*].

Primary hyperaldosteronism (adrenal tumor) was discovered in a patient who had been observed in a mental institution for twenty-five years because of schizophrenia. Nocturnal polyuria with enuresis led to the investigation. A remarkable reversal of normal diurnal variation in the urinary excretion of salt and water was found. Renal concentrating ability was only minimally impaired. The studies reported were directed primarily at examining this unusual diurnal rhythm and the role of posture in its genesis.

METHODS

When special studies were undertaken two basic diets were used. During the brief period when a very low sodium intake was necessary, the patient was fed a dialyzed milk product (Lonalac®) supplying 2.1 mEq. sodium and 61.8 mEq. potassium daily (based on the analysis of the manufacturer). Sufficient carbohydrate was added to provide 1,500 calories daily.

A second, more palatable diet supplied an average daily intake of 15 mEq. sodium, 79 mEq. potassium and 1,800 calories. Aliquots of the homogenized food from weighed, duplicate trays (corrected for uneaten portions) were digested with nitric acid [*2*] and analyzed for sodium and potassium. When higher intakes were required, sodium (as the chloride salt) and potassium (as Potassium Triplex®) were added.

Because the patient could not cooperate, all urine specimens were collected by inlying catheter.

Sodium and potassium in serum, urine, saliva and food were determined with an internal standard flame photometer. Osmolarity of serum and urine was obtained with a Fiske freezing point osmometer. Urinary 17-ketosteroids were determined by the Callow-Zimmerman method using absolute alcohol and employing a color correction equation [*3*]. Urinary corticosteroids were determined by the sodium bismuthate method of Norymberski [*4,5*]. Urinary catechol amines were estimated by bioassay [*6*]. Chloride in serum and urine was measured by a modification of Whitehorn's method [*7*]. The remaining serum and urine chemical determinations were made by standard methods [*8*].

CLINICAL AND LABORATORY STUDIES

The patient was a forty-seven year old white woman who was transferred to the Milwaukee County General Hospital from the Milwaukee County Hospital for Mental Diseases for study because of nocturnal polyuria. The past history revealed that paranoid delusions were noted at twenty-three years of age (1935). She was committed to the hospital with a diagnosis of paranoid schizophrenia. Other than for brief and unsuccessful periods of trial release, she had been continuously hospitalized.

In 1935 she was described as a well developed and nourished white woman, 5 feet 5 inches tall, weighing 109 pounds. The blood pressure was 105 mm. Hg systolic and 68 mm. Hg diastolic. No physical abnormalities were described. Urinalysis revealed an acid urine with a specific gravity of 1.025. Results of tests for albuminuria and glycosuria were negative.

Her health was apparently good during most of her long hospitalization. The hospital records make no mention of signs or symptoms of cardiac, hepatic or renal disease other than as noted subsequently. Episodic weakness, tetany, edema or diarrhea were never noted. Laxatives were rarely administered.

Prior to insulin shock therapy in 1939 (at twenty-eight years of age), a glucose tolerance test was performed. A diabetic curve was found (blood sugar 172 mg. per cent two hours after the administration of

* From the Department of Medicine, Marquette University School of Medicine and the Milwaukee County Hospital, Milwaukee, Wisconsin. This study was supported in part by grants (No. 2A–5026, A–1200) from the U. S. Public Health Service.

TABLE I
INITIAL LABORATORY VALUES AND RESULTS OF ROENTGENOGRAPHIC TESTS

Fasting blood sugar (mg. %)	101.0
Non-protein nitrogen (mg. %)	22.8
Sodium (mEq./L.)	141.0
Potassium (mEq./L.)	2.0
Chloride (mEq./L.)	102.0
Bicarbonate (mEq./L.)	32.8
Calcium (mg. %)	10.1
Phosphorus (mg. %)	3.8
Total protein (gm. %)	7.3
Albumin (gm. %)	4.5
Globulin (gm. %)	2.8
Hemoglobin (gm.)	12.0
White blood count (per cu. mm.)	10,950
X-rays of the skull, chest, long bones and hands	No abnormalities
Intravenous urogram	No abnormalities
Tomograms of the abdomen	No abnormalities

TABLE II
RESULTS OF RENAL FUNCTION STUDIES BEFORE SURGERY

Test	Supine
Phenolsulfonphthalein (%)	
30 min.	45
1 hr.	25
Total	70
Renal blood flow (cc./min.)	798
Renal plasma flow (PAH) (cc./min.)	463
Glomerular filtration rate (mannitol) (cc./min.)	88.6
Filtration fraction	0.19

glucose). The diet prior to the test and the dosage and route of glucose administration were not specified. There was no family history of diabetes. Treatment consisted of convulsant therapy with insulin and Metrazol.® Some temporary improvement in her mental status was described.

Blood pressures recorded during annual examinations were normal until 1947 (at thirty-five years of age) when the systolic pressure was 142 mm. Hg and the diastolic, 96 mm. Hg. Mild hypertension persisted for the next five years, but from 1952 more severe hypertension was present, the systolic pressure being consistently over 160 mm. Hg and the diastolic over 100 mm. Hg.

Sporadic urine specimens voided in the morning were examined during her stay in the mental hospital. It is of interest that since 1950 (at thirty-eight years of age), the urine had tended to be alkaline and of relatively low specific gravity. These data suggest that hyperaldosteronism originated when the patient was about thirty-five to thirty-eight years of age and about ten years before our studies.

When forty-one years old (1953), the patient was noted to urinate three to ten times each night, frequently with enuresis. The patient was seen in consultation by the urological service. The blood nonprotein nitrogen was normal. Cystoscopy, a cystometrogram and an intravenous urogram revealed no abnormalities. No diagnosis was established.

In 1957, Dr. Ruth Jansen of the staff of the Hospital for Mental Diseases referred the patient (age forty-five) to the General Hospital for evaluation, noting persistent nocturia and the excretion of a concentrated urine while up and about (specific gravity 1.021 to 1.025) and a dilute urine while at rest in bed (specific gravity 1.004 to 1.013).

Physical examination revealed persistent hypertension (systolic pressure 170 to 190 mm. Hg, diastolic 110 to 120 mm. Hg) and moderate alteration of the retinal vessels (narrowing of arterioles, increased arteriolar light reflex, and venous displacement and compression at arteriolar crossings). The heart was not clinically enlarged. There was no edema and no signs of increased venous pressure were noted. The patient weighed 122 pounds. Her strength seemed normal. Chvostek's and Trousseau's signs could not be elicited. The remainder of the examination was non-contributory.

Initial laboratory and radiologic data are listed in Table I. Ventilatory and flow rate studies indicated normal pulmonary function. Prominent U waves were present in an electrocardiogram.

The blood pressure was not significantly affected by postural changes. Deep sedation with barbiturates failed to reduce the degree of hypertension. The urinary excretion of catechol amines was normal on two occasions. The blood glucose was 160 mg. per cent two hours after ingesting 50 gm. of glucose. Glycosuria was not found.

General studies of renal function are summarized in Table II. There was minimal if any impairment of urine concentration (maximal concentration of random morning specimens without enforced water deprivation was 889 mOsm. per L.). Renal blood flow and glomerular filtration rate were moderately decreased. Although the urine was usually neutral to faintly alkaline, the patient was able to excrete a urine of pH 5 when challenged with the administration of oral ammonium chloride. Mild proteinuria (mean 0.38 gm. daily) was consistently present. No organisms were grown on urine culture.

When on a general hospital diet and while the serum potassium ranged from 2 to 3.2 mEq. per L., the urinary excretion of potassium was inappropriately high (mean of five days determinations, 45 mEq. per day). Twenty days of potassium supplementation (120 mEq. per day in addition to a general diet) produced a maximum serum potassium of 3.8 mEq. per L.

When dietary sodium was sharply restricted (2.1 mEq. per day) on the Lonalac® diet, the urinary

potassium averaged 22.7 mEq. daily. Urinary sodium during the last four days of this five day period averaged 3.0 mEq. per day. Abrupt increase of the intake of sodium (215 mEq. per day) resulted in a mean potassium excretion of 60 mEq. daily. A lesser sodium intake (151 mEq. daily) resulted in a proportionately smaller mean value for potassium excretion (47.5 mEq. per day). These data are illustrated in Figure 1.

Salivary sodium and potassium were determined on four mid-morning specimens while the patient was on a diet containing 151 mEq. of sodium and 79 mEq. potassium. Although normal values for salivary sodium and potassium vary widely in different laboratories, a mean salivary sodium of 6.95 mEq. per L. and salivary potassium of 32.2 mEq. per L. while on a normal intake of salt strongly suggested the influence of a salt-retaining hormone.

The serum bicarbonate ranged from 24 to 34 mEq. per L. in a manner not systematically related to the serum potassium or manipulations of the diet.

Urinary 17-ketosteroids were 4.9, 4.7 and 3 mg. per twenty-four hours on three separate collections (all low normal values in this laboratory). Simultaneously determined urinary corticosteroids (ketogenic) were 3.9, 5.7 and 3.3 mg. per twenty-four hours (normal values). A three day intramuscular ACTH test [*9*] resulted in peak 17-ketosteroid excretion of 18.5 mg. and peak corticosteroid excretion of 43.7 mg. per twenty-four hours. Sodium was retained during the first two days of the administration of ACTH, but on the last day the urinary sodium excretion exceeded sodium intake by 111 mEq.

The urinary excretion of aldosterone (kindly assayed by Dr. Jerome Conn) was 24 μg. per day (twice the highest normal values obtained in Dr. Conn's laboratory) while the patient was on a diet containing 151 mEq. of sodium and 76 mEq. of potassium per day.

The patient was given a diet low in sodium (14 mEq. per day) and high in potassium (194 mEq. per day) for ten days, and following preparation with cortisone (150 mg. administered intramuscularly) on the night before and the morning of surgery, an exploratory laparotomy was performed (Dr. E. Ellison).

FINDINGS AT SURGERY AND POSTOPERATIVE COURSE

On exposing both adrenals through a long midline abdominal incision a tumor, 2 cm. in diameter, was found at the upper pole of the left adrenal gland. The left adrenal itself appeared somewhat enlarged. The right adrenal appeared somewhat small, but not definitely atrophic. The left adrenal and attached tumor were removed *en bloc* and the right adrenal was left undisturbed. The remainder of the abdominal viscera were normal to inspection and palpation. Bilateral needle biopsies of the kidneys were obtained and a small wedge of liver excised for examination. The patient tolerated the procedure without event.

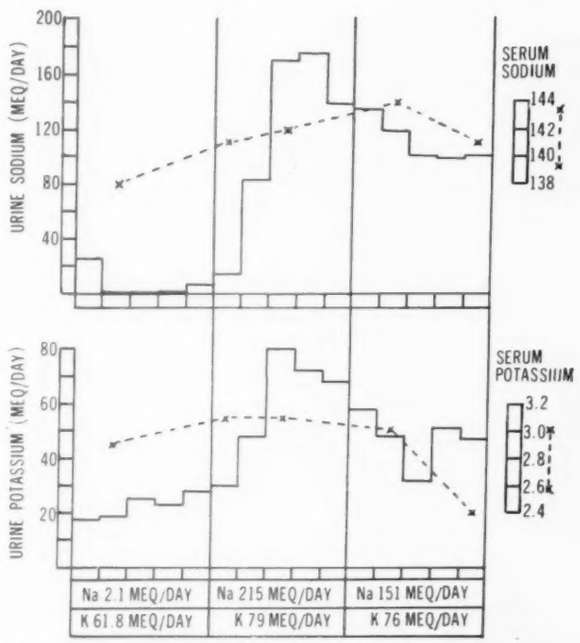

FIG. 1. The preoperative urinary excretion of sodium and potassium on varying intakes of sodium, but with the intake of potassium held relatively constant. (Each small box on the abscissa equals one day.)

The left adrenal with attached tumor weighed 10 gm. A nodule measuring 2 by 2.5 by 2 cm. was noted in the central portion of the gland. Pathologic diagnosis (Dr. Paul Kimmelstiel) was "adrenal cortical adenoma," the remainder of the adrenal tissue being normal. Biopsy specimens of the kidney and liver showed no specific or diagnostic changes. In particular, the renal proximal convoluted tubules appeared normal.

The dosage of cortisone was progressively and rapidly decreased. On the fifth postoperative day, having received 25 mg. of cortisone the preceding day and 12.5 mg. that day, a sudden massive gastrointestinal hemorrhage occurred. This responded to medical management and after several hectic days no further difficulties were encountered.

The serum potassium rose to 3.9 mEq. per L. on the morning after surgery and has remained 4 mEq. per L. or above since the third postoperative day. An accurate potassium balance could not be kept because of the gastrointestinal hemorrhage.

Four months postoperatively the blood urea nitrogen was 19 mg. per cent. The serum electrolytes (in mEq. per L.) were: sodium 141, potassium 4.3, chloride 104 and bicarbonate 24.6. Urinary 17-ketosteroids were 4.8 mg. per twenty-four hours and urinary cortins 1.8 mg. per twenty-four hours (normal values in this laboratory). A glucose tolerance test showed that the patient still had diabetes (two hour value 140 mg. per cent). The hypertension was considerably improved but persisted (mean blood pres-

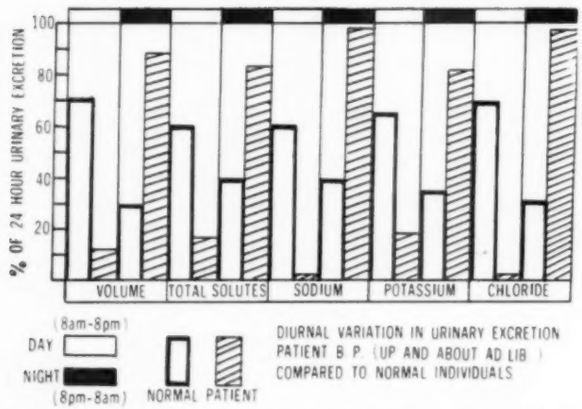

FIG. 2. The preoperative diurnal variation in the urinary volume and content of total solutes, sodium, potassium and chloride compared to normal subjects.

sure on ten consecutive days was 154 mm. Hg systolic and 94 mm. Hg diastolic compared to a mean blood pressure of 172 mm. Hg systolic and 105 mm. Hg diastolic before surgery). An electrocardiogram was normal. The personnel at the Hospital for Mental Diseases believed that the patient had become more alert, had less delusions and was more accessible.

Although Escherichia coli organisms were present in the urine for a short time postoperatively, urine cultures became sterile after a course of chloramphenicol. The urine was usually weakly acid. The patient customarily voided once rather than several times at night.

When the patient was given a diet containing 15 mEq. of sodium and 80 mEq. of potassium, the urinary excretion of sodium declined to equal the intake by the fourth day. The mean (four day) potassium excretion was 50.4 mEq. per day. When the sodium intake was increased to 215 mEq. per day (potassium intake held constant) somewhat less potassium was excreted in the urine (mean of four days, 42.4 mEq. per day).

STUDIES OF THE URINARY DIURNAL RHYTHM

Prior to operation, the diurnal variation in the urinary excretion of water, sodium, chloride, potassium and total solutes was examined. Urine specimens were collected from 8 A.M. to 8 P.M. (day specimen) and from 8 P.M. to 8 A.M. (night specimen). Day-night fractions were collected for seven days while the patient followed her usual pattern of ambulation and sleep, and while the diet provided 151 mEq. of sodium and 80 mEq. of potassium daily. The patient's mean day-night excretory pattern (expressed as per cent of the twenty-four hour urinary output) to the mean values obtained by others in five normal, ambulatory

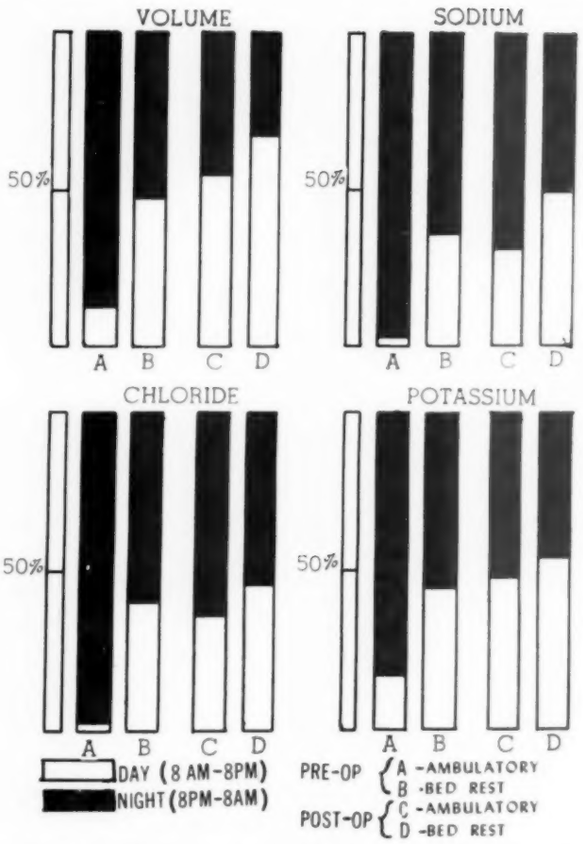

FIG. 3. The effects of posture on the diurnal variation in the urinary volume and content of sodium, chloride and potassium before and four months after removal of the adrenal adenoma. Each bar represents the mean values for four or more twenty-four hour collections (see text) and compares the per cent of the total twenty-four hour output excreted by day and by night.

subjects (derived from the data of Payne and de Wardener [*10*]) are compared in Figure 2. A marked reversal of the normal diurnal variation in the excretion of all substances studied is clearly shown.

The patient was then kept at bed rest for five periods (each twenty-four hours in length). The diet was held constant and urine specimens were collected in the same manner. Under these circumstances there was a considerable increase in the percentage of water, sodium, chloride and potassium excreted during the day. (Fig. 3.)

Four months after surgery these studies were repeated. An identical diet was given and urine was collected in the same manner during five days of normal activities and four days of complete bed rest. The results of these experiments are shown in Figure 3. It is apparent that bed rest prior to surgery produced values similar to

TABLE III*

THE EFFECTS OF LEG WRAPPING, ALCOHOL AND MERCURIALS ON THE EXCRETION OF A WATER LOAD IN THE SUPINE POSITION AND DURING QUIET STANDING BEFORE SURGERY

Data	Supine		Quiet Standing	
	Water Load Excreted from 8 A.M. to 12 P.M. (%)	Peak Urine Flow (cc./min.)	Water Load Excreted from 8 A.M. to 12 P.M. (%)	Peak Urine Flow (cc./min.)
1,000 cc. tap water orally from 8 to 9 A.M.	144	19.1	34	2.6
1,000 cc. tap water orally from 8 to 9 A.M. plus Ace bandages on legs	129	16.8	42	6.5
1,000 cc. tap water orally from 8 to 9 A.M. plus 1,000 cc. 5% glucose in water with 5% alcohol from 9 to 9:45 A.M.	88	18.7	73	10.1
1,000 cc. tap water orally from 8 to 9 A.M. plus 2 cc. Mercuhydrin® intramuscularly at 6 A.M.	...	...	126	11.4

* All values given are the mean of two or more experiments.

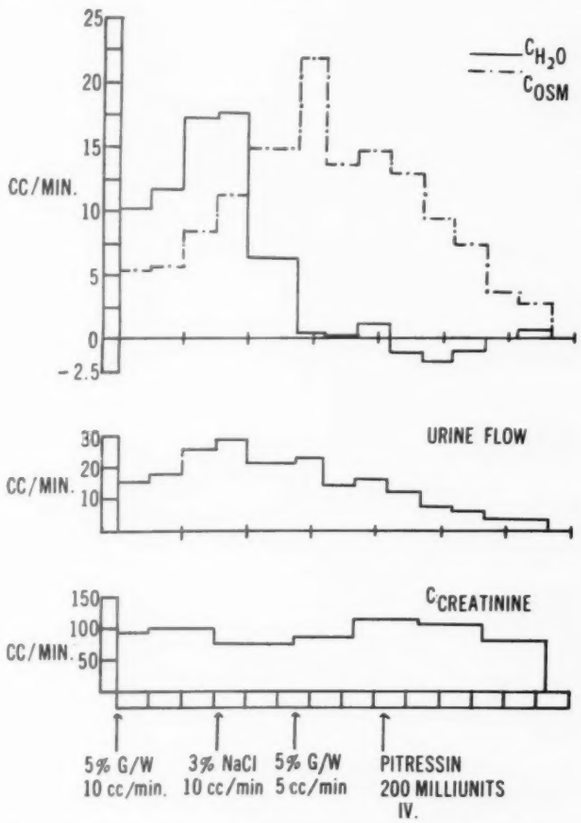

FIG. 4. Results of water loading and hypertonic saline infusion in the supine position before surgery. (Each box on the abscissa equals fifteen minutes.) One liter of tap water was given orally at minus 60 minutes.

those found during ambulation after the adenoma was removed.

Because posture seemed an important factor in the production of the disturbed diurnal rhythm, the effects of posture on the excretion of salt and water loads was investigated prior to surgery in a series of acute experiments. All experiments were performed in the morning after a twelve hour period of food and water deprivation.

When supine, an oral load of 1,000 cc. of tap water was quantitatively excreted within one hour, and by four hours an additional 442 cc. of water was excreted. When standing quietly, only about one-third of the administered load was recovered in four hours. The values obtained in the upright position were moderately increased by reducing venous stasis in the legs (elastic bindings) and closely approximated those obtained when supine if alcohol or mercurials were given. These studies are summarized in Table III.

To clarify further the renal handling of water and salt loads, more detailed studies were made of the effects of the administration of intravenous water loads and of hypertonic saline infusion while supine and while tilted to a head-upright position of 20 degrees. (Figs. 4 and 5.) A liter of tap water was ingested as rapidly as possible at 7 A.M. An hour later the bladder was emptied and an infusion of 5 per cent glucose in water was begun at 10 cc. per minute. Comparable peak rates of osmotically unobligated ("free") water clearance were produced when supine (17.4 cc. per minute) and at the slight head-up tilt (15.5 cc. per minute). When supine, the infusion of 3 per cent sodium chloride resulted in a slow decline in urine flow, a sharp increase in osmolar clearance, and marked increases in the excretion of sodium, potassium and chloride. Free water clearance fell. An osmotic urine/plasma ratio of 1 was reached forty-seven minutes after beginning the hypertonic saline infusion. The intravenous administration of 200 milliunits of vasopressin (Pitressin®) resulted in a slight further rise in the osmotic U/P ratio (1.23). When in the 20 degree head-upright tilt, hypertonic saline

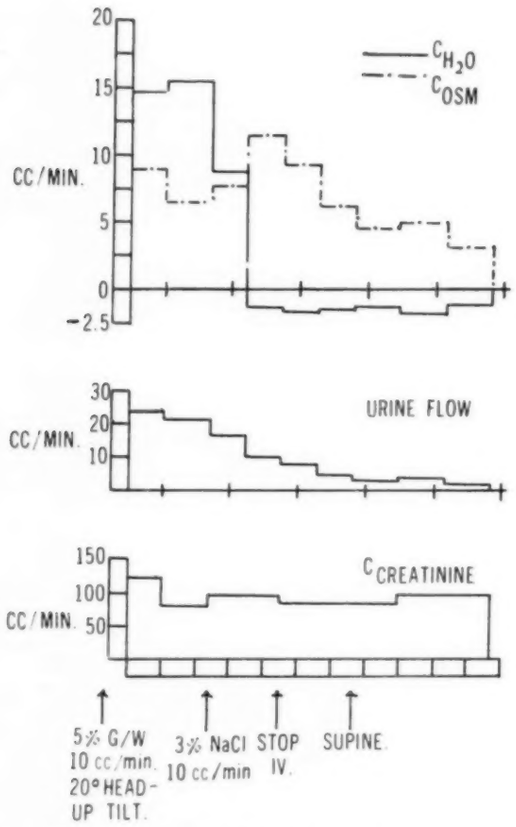

FIG. 5. Results of water loading and hypertonic saline infusion with the patient placed at a 20 degree head-upright tilt before surgery. (Each box in the abscissa equals fifteen minutes.) One liter of tap water was given orally at minus 60 minutes.

infusion caused a more prompt decline in the urine flow, a much smaller increase in osmolar clearance and in the excretion of sodium, potassium and chloride, and a more prompt and pronounced decline in free water clearance. The osmotic U/P ratio exceeded 1 within thirty minutes of the start of the hypertonic saline infusion.

The saluresis induced by the hypertonic saline infusion in the two positions is shown graphically in Figure 6. When supine, sodium was excreted at a peak rate of 2,690 mEq. per minute. When tilted to a head-upright position of 20 degrees, the peak rate of sodium excretion was 1,420 mEq. per minute.

The clearance of endogenous creatinine during the two experiments varied moderately. A moderate fall in creatinine clearance was noted in both experiments when the hypertonic saline infusion was begun. Mean creatinine clearance was practically identical in the two positions

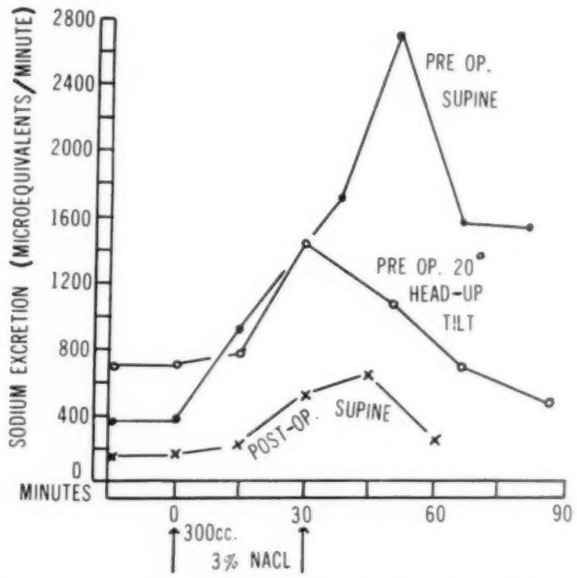

FIG. 6. The effects of tilting to the head-upright position and removal of the adrenal adenoma on the renal excretion of sodium.

(90.9 cc. per minute while supine, 91.5 cc. per minute while tilted to a head-up position).

A similar study was attempted with a cardiac catheter and Cournand needle in place to observe simultaneously the effects of tilting on systemic blood pressure, right atrial and pulmonary wedge pressures, and the renal excretion of salt and water. Unfortunately, the patient became unmanageably apprehensive, limiting the data which could be obtained. The pressure measurements obtained and the calculated hemodynamic data are summarized in Table IV. Main pulmonary and right atrial arterial oxygen values were normal and were not significantly affected during the tilting procedures. The patient would not breathe through a mouthpiece or mask; therefore standard tables were used to calculate cardiac outputs, assuming that lying at a 20 degree head-upright tilt involved no work by the patient. The patient had received oral and intravenous water loads prior to the pressure recordings, probably explaining the slightly elevated pressures in the superior vena cava and right atrium and the moderately increased cardiac output. When the patient was placed in a 20 degree head-upright tilt, there was a moderate fall in systemic blood pressure (22 mm. Hg systolic, diastolic unchanged) and a significant fall in right heart and venous pressures and in cardiac output. Calculated left ventricular work was elevated, primarily because of the systemic

TABLE IV

THE EFFECTS OF TILTING ON CARDIAC WORK AND INTRACARDIAC PRESSURES

Location and Test	Supine		20° Head-up Tilt	
Pressure Measurements (mm. Hg)				
	Systolic/Diastolic	Mean	Systolic/Diastolic	Mean
Superior vena cava	11/5	7.5	...	...
Mid-right atrium	11/3	7.0	0/−5	−2.0
Right ventricle	37/3	11.0	14/−5	...
Right pulmonary artery wedge	...	9.0	...	7.0
Main pulmonary artery	35/5	16.0	14/−1	7.0
Right brachial artery	210/105	140.0	188/105	128.0
Hemodynamic Calculations				
Systemic blood flow (L./min.)	5.76		4.52	
Cardiac index (L./min./M²)	3.60		2.83	
Left ventricular work (kg. M/min.)	11.0		7.9	
Right ventricular work (kg. M/min.)	1.3		0.3	
Systemic vascular resistance (dyne/sec./cm.$^{-5}$)	1852		2300	
Pulmonary vascular resistance (dyne/sec./cm.$^{-5}$)	28			

hypertension. It fell to a normal range during the 20 degree tilt. In spite of a fall in systemic blood pressure, the already elevated systemic vascular resistance increased further during the 20 degree tilt study. Calculated right ventricular work was at the upper limits of normal in the supine position and decreased in a normal fashion during the tilt. Pulmonary vascular resistance was well within the normal range throughout the entire catheterization procedure. When the patient was placed in a 70 degree head-upright tilt, syncope developed in twelve minutes and it was necessary to return her to a 20 degree tilt. The pressures listed in Table IV were not recorded until the patient had stabilized in the latter position.

The renal studies carried out during these procedures are presented in Figure 7. They are of limited value because of the extraneous factor of apprehension. Urine excretion (already declining, presumably because of fright) fell further when the patient was placed in a 70 degree head-up tilt. The initial fall was due primarily to a decline in glomerular filtration rate, the osmotic U/P ratio remaining low. When syncope occurred, the osmotic U/P ratio rose sharply and remained high for fifty minutes of observation, even when glomerular filtration rose after return to the supine position. Osmolar

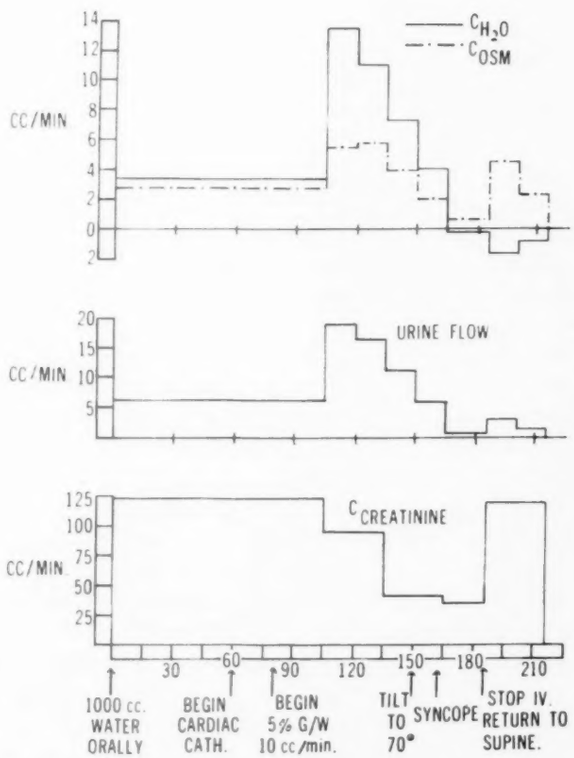

FIG. 7. Free water clearance (C_{H_2O}), osmolar clearance (C_{OSM}), urine flow and creatinine clearance during cardiac catheterization studies.

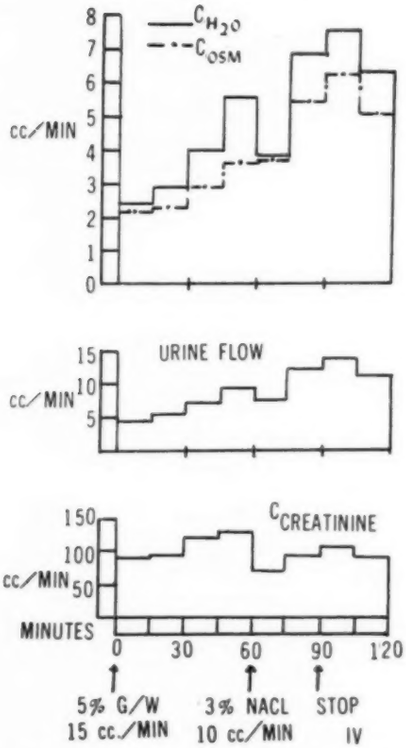

FIG. 8. Results of water loading and hypertonic saline infusion four months after removal of the adrenal adenoma.

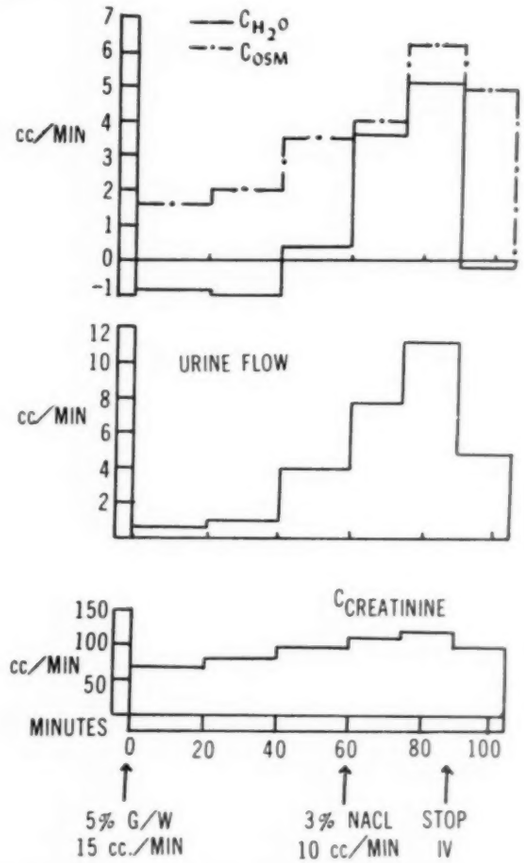

FIG. 9. The renal response to a smaller water load followed by hypertonic saline infusion four months after surgery.

clearance fell during the tilt and rose again when the supine position was resumed.

Four months after surgery the effects of water loading and hypertonic saline infusion were again studied in the supine position. (Fig. 8.) A liter of tap water was given at 7 A.M. and at 8 A.M. the bladder was emptied and an infusion of 5 per cent glucose in water was begun at 10 cc. per minute. Although the infusion was continued for sixty minutes, peak free water clearance rose to only 5.6 cc. per minute. When 3 per cent sodium chloride was then infused, urine flow, free water clearance and creatinine clearance all initially fell, and then rose again. Free water clearance reached a value of 7.5 cc. per minute fifteen minutes after the hypertonic saline infusion was completed. Osmolar clearance rose moderately after hypertonic saline solution was infused. The peak rate of sodium excretion (620 mEq. per minute) was less than one-fourth the value noted during a similar experiment before surgery. The clearance of endogenous creatinine was similar to that noted prior to operation. It was believed that the apparent failure of hypertonic saline solution to induce antidiuresis in this experiment (which was repeated with similar results) was due to the slow excretion of the water load with consequent stimulation of volume receptors suppressing the release of antidiuretic hormone. An additional experiment was therefore performed. (Fig. 9.) The priming load of tap water was omitted and 5 per cent glucose and water was infused at 15 cc. per minute for sixty minutes. Hypertonic saline solution was then infused, with an initial increase in free-water clearance but a prompt antidiuretic response immediately after the salt infusion was stopped, confirming our initial impression.

COMMENTS

The general features of primary hyperaldosteronism and the variations in reported cases have been reviewed elsewhere [*11–13*]. Absence of episodic weakness, failure to demonstrate latent tetany, relatively mild hypokalemia and alkalosis, and mild impairment of renal function (including concentrating ability) are not entirely unique findings.

Direct evidence of increased aldosterone production was obtained by urine assay. A persistently low salivary Na/K ratio gave indirect evidence of the action of a salt-retaining hormone. Potassium excretion in the urine was clearly inappropriately high [*14*]. The ability of the renal tubules to excrete an acid load, to excrete phenolsulfonphthalein dye, to conserve sodium and to concentrate the urine suggested that potassium wasting was not due to a primary tubular defect. Potassium excretion decreased when dietary sodium was restricted and rose sharply when sodium intake was increased. This suggested that potassium excretion was directly related to the amount of sodium reaching the distal tubule for ion exchange and that the tubules were continuously influenced by a salt-retaining hormone. Postoperatively, the urinary excretion of potassium was slightly higher when dietary sodium was restricted, suggesting that salt restriction stimulated the remaining adrenal to secrete more aldosterone, as in normal persons.

A marked disturbance of the diurnal rhythm of urine formation was of particular interest. This consisted of far greater urinary excretion of water, sodium, chloride, potassium and total solutes during the night. Keeping the patient at bed rest tended to correct this disturbance, implicating posture in its production. Postural hypotension was not observed except during the cardiac catheterization studies (at a passive 70 degree tilt). After removal of the adrenal adenoma, the diurnal rhythm of urine formation more closely approximated normal, although sodium and chloride were still excreted largely during the night.

Water diuresis was exaggerated when supine and impaired when standing upright. As in normal subjects [*15,16*], the antidiuresis of quiet standing was partially eliminated by leg wrapping and nearly abolished when alcohol was given. This suggested that the antidiuresis observed was produced by the antidiuretic hormone in response to a decrease in effective blood volume. The exaggerated effects of posture in the patient suggested an unusually sensitive volume-regulating system.

When hypertonic saline solution was infused after initiating a water diuresis with the patient supine (before surgery), brisk urine flow persisted. Skanse et al. [*17*] reported a similar response in a patient with primary hyperaldosteronism and suggested that the saline infusion might not have sufficiently altered serum osmolarity (since the patient already had hypernatremia) to cause antidiuretic hormone release. However, in the present case further analysis prior to surgery indicated that hypertonic saline infusion indeed produced conservation of osmotically unobligated water, but a great increase in osmolar clearance resulted in continued high urine flow. Thus, osmoreceptor control of antidiuretic hormone release was intact. The renal tubules were responsive to exogenous as well as endogenous vasopressin. Urine osmolalities as high as 889 mOsm. per L. were noted in urine specimens collected during the day. Postoperatively, hypertonic saline infusion after water loading produced no significant fall in free water clearance if the water load was large, but a decided fall if a smaller water load was given. This suggested that osmoreceptor control of antidiuretic hormone was intact but easily suppressed by volume expansion.

Before surgery a 9 gm. sodium chloride load was completely excreted in ninety minutes while supine, but when tilted to a head-up position of 20 degrees less than a half of an identical load was eliminated in ninety minutes. This degree of tilt did not significantly alter water diuresis, the rate of sodium excretion during water loading, blood pressure or creatinine clearance. Dingman et al. [*18*] observed abnormal increases in salt excretion when hypertonic saline solution was given to a patient with primary hyperaldosteronism during hydropenia. Dustan, Corcoran and Page [*19*] induced abnormal degrees of saluresis in patients with this syndrome by infusing para-aminohippuric acid and mannitol. It seemed clear that volume expansion was the factor inducing exaggerated saluresis in the present case. After removal of the adrenal adenoma this response was not observed in the supine position.

The patient's response to salt and water loading in various positions suggested that two opposing mechanisms were present: First, presumptively aldosterone, promoting salt retention (and secondarily, via osmoreceptor stimulation of antidiuretic hormone, water retention) and secondly, an unidentified mechanism limiting expansion of the body fluids by promoting the excretion of salt and water (in ratios which maintained or restored serum osmolarity). As a consequence, effective vascular volume was permitted to vary over a narrow range. Thus during the day, when the effective vascular

volume was reduced by blood-trapping in dependent portions of the body, salt and water (equivalent to about 500 to 1,000 cc. of isotonic saline) were retained. When lying down at night the reverse occurred and salt and water were excreted. This appeared to be the mode of production of the disturbed diurnal urinary rhythm. In addition, a mechanism limiting volume expansion could account for: (1) the absence of edema in this and most other cases of primary hyperaldosteronism; (2) "escape" from sodium retention during the administration of large doses of aldosterone to normal subjects [*20*]; and (3) "paradoxical" sodium excretion when patients with primary hyperaldosteronism are given adrenocorticotrophic hormone [*21*].

The nature of this volume-sensitive system can only be speculative at present. Although our data do not show significant changes in systemic blood pressure or in the clearance of endogenous creatinine during the tilting procedures (except as noted during the cardiac catheterization studies) or after surgery, it is clear that they do not exclude local renal hemodynamic changes. More refined measurements of these parameters will be required.

A number of alternate possibilities remain. We have no data to exclude posturally-induced changes in aldosterone secretion during the reported studies. However, the known lag in aldosterone action, even when injected directly into the renal artery [*22*], makes it difficult to accept changes in the rate of aldosterone secretion as the cause of the marked differences in sodium excretion observed in the acute infusion studies before surgery. Finally, the coexistence of hyperaldosteronism and a disturbed diurnal urinary rhythm does not necessarily imply a cause and effect relationship nor, if such a relationship holds, does it indicate which defect is primary. Four months after removal of the adrenal adenoma the diurnal urinary rhythm had changed markedly but was not completely restored to normal. If the disturbance in renal excretory rhythm was primary and hyperaldosteronism was, in some manner, a compensatory mechanism, further exaggeration of the disturbance in diurnal rhythm after surgery might be expected. If the two phenomena were unrelated or both the result of a distant cause (disturbance in volume regulation) the course of events observed may have been an entirely non-specific response. If hyperaldosteronism was primary and induced the disturbance in urinary diurnal rhythm, it is necessary to postulate that (1) some degree of irreversibility now exists, (2) sufficient time has not elapsed to allow complete recovery, or (3) hyperaldosteronism still exists (in spite of the decline of blood pressure and restoration of potassium balance). The latter two possibilities seem unlikely but remain to be finally evaluated.

SUMMARY AND CONCLUSIONS

A patient with primary hyperaldosteronism excreted more water, sodium, chloride, potassium and total solutes in the urine during the night than during the day. This reversed diurnal rhythm was considerably corrected by bed rest and further corrected following removal of the adrenal adenoma.

Volume expansion in the supine position produced exaggerated water and/or salt excretion, depending on the composition of the expanding fluid. Standing or tilting the patient to a head-up position greatly reduced these responses. Following surgery, diuretic and saluretic responses were markedly reduced.

A volume-limiting mechanism seems to oppose aldosterone by promoting salt and water excretion when effective vascular volume reaches a critical upper limit. The reversed urinary diurnal rhythm observed would then have resulted from changes in the effective vascular volume produced by changes in posture. A mechanism of this type could also explain the absence of edema and the ACTH-induced saluresis in patients with primary hyperaldosteronism as well as the "escape" from sodium retention occurring in normal subjects given aldosterone.

Nocturnal polyuria noted in other cases of primary hyperaldosteronism may have been produced by postural phenomena similar to those reported here.

Acknowledgment: We are indebted to the helpful advice of Drs. Arnold Relman and Franklin Epstein. Dr. John Huston kindly performed the cardiac catheterization and interpreted the data obtained. These studies would have been impossible without the skilled technical assistance of Miss Opal Kelly, Miss Bernadette Klapinski and Mrs. Dolores Gonyo.

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Precipitating Antifibrinogen Antibody Appearing After Fibrinogen Infusions in a Patient with Congenital Afibrinogenemia*

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SINCE the description of "Faserstoffmangel im Blute" by Rabe and Salomon in 1920 [*1*], over thirty cases of congenital afibrinogenemia have been reported. The clinical and laboratory features of this hereditary familial disease have been extensively reviewed by Frick and McQuarrie [*2*]. It has been demonstrated by Gitlin and Borges [*3*] that the lack of fibrinogen in this condition is due to a disturbance in synthesis and not to an increased rate of degradation.

Congenital afibrinogenemia is a serious disease; although blood and plasma transfusions or fibrinogen infusions are able to tide the patients over acute hemorrhagic phases and surgical interventions, only a few patients have reached the age of twenty [*2*].

In the present study we report a complication of fibrinogen therapy, formation of antifibrinogen antibody and severe reactions to fibrinogen infusion in a patient with congenital afibrinogenemia; the appearance of the antibody was associated with a marked increase in the turnover rate of plasma fibrinogen, thus decreasing the hemostatic effectiveness of the infused fibrinogen. The development of antifibrinogen antibody after transfusion in a patient with congenital afibrinogenemia had been previously reported by Brönnimann [*4*].

CASE REPORT

C. M., a sixteen year old native Israeli girl, was admitted to our department for the first time on January 4, 1959, with a painful and swollen left knee. There was no history of trauma.

From an early age the patient had had spontaneous and traumatic hemorrhages in the skin; once, after having cut her hand, bleeding continued for many hours. At the age of nine she had acute tonsillitis followed by a prolonged period of febrile illness, and rheumatic fever was diagnosed. She developed well and was active in school. At the age of thirteen she had her menarche. Menstruation had always been normal.

Her parents, who are cousins, are healthy. One brother died three days after birth from umbilical bleeding. A sister suffered easy bruising and hemarthroses from an early age and died of cerebral hemorrhage at the age of nineteen. Three brothers and two sisters are apparently healthy and have no history of bleeding. Examination of the blood of the mother, one brother and one sister showed normal clotting times and fibrinogen levels.

Physical examination showed a well developed girl in fair nutritional condition. Her temperature was normal, the blood pressure was 110/70 mm. Hg. The head, neck and lungs were normal. Examination of the heart revealed the maximum impulse in the sixth intercostal space at the mid-clavicular line and an apical systolic thrill was felt. The rhythm was regular. There was right ventricular systolic uplift. The first sound at the apex was loud. An apical grade 3 systolic murmur and a diastolic murmur filling the early and middle period of the diastole were heard. The second sound over the pulmonic area was accentuated and reduplicated. The aortic sounds were normal. The liver was not palpable. The spleen was felt 1 cm. below the costal margin, it was firm and non-tender. The left knee was swollen, warm and red and after a few days showed blue discoloration. Roentgen examination of the heart showed a mitral configuration with enlargement of the left atrium. The electrocardiogram was normal.

Laboratory data revealed a normal urine, a hemoglobin of 11.3 gm. per cent, a red blood cell count of 3,600,000 per cu. mm., a white cell count of 10,000

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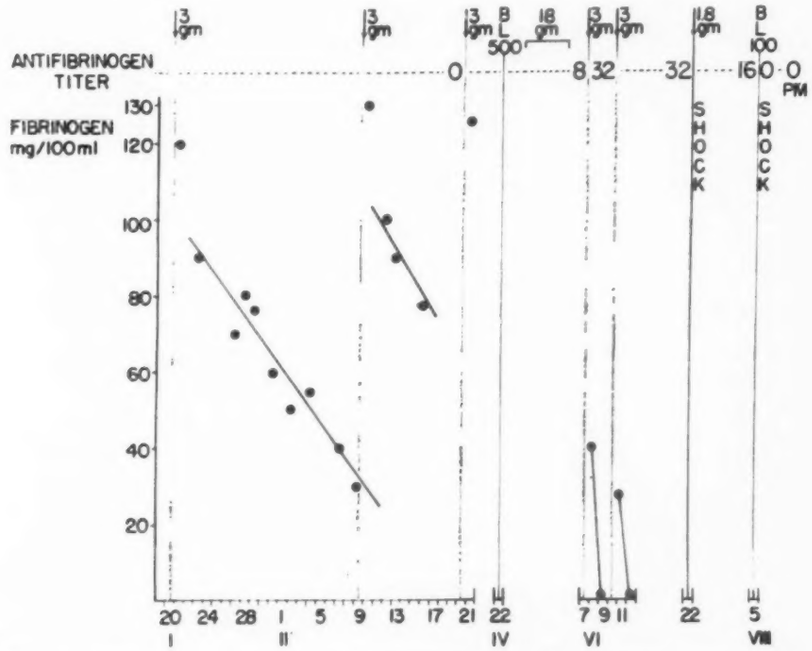

FIG. 1. Disappearance curves of fibrinogen from plasma after intravenous administration of human plasma fraction I to patient with congenital afibrinogenemia, before and after appearance of antifibrinogen antibody. Antifibrinogen titers left of vertical lines refer to plasma samples obtained immediately preceding fibrinogen infusion; right of the line on August 5 immediately after infusion; PM postmortem blood.

per cu. mm. with a normal differential count, and platelets 150,000 per cu. mm. The serum total proteins were 6.9 gm. per cent, albumin 4.2 gm. per cent; the paper electrophoretic pattern was normal. C-reactive protein was absent and the antistreptolysin titer was zero. The erythrocyte sedimentation rate was 0 mm. in the first hour. The bleeding time (Duke's method [5]) was two minutes, the vascular fragility test (Rumpell-Leede) normal. The blood did not clot for an indefinite period of time, also not when thromboplastin or thrombin was added. The plasma prothrombin (one-stage method of Quick [5]) was 80 per cent; the plasma accelerin [5], the thromboplastin generation (method of Biggs and Douglas [6]) and the antithrombin [5] were normal. The plasma had no increased fibrinolytic activity, the profibrinolysin was normal (method of Loomis [7]). There was no circulating anticoagulant (method of Quick [5]). The diagnosis of congenital afibrinogenemia was made.

On January 18, two weeks after admission, the patient had a subfebrile temperature up to 37.6°C. On January 20 she was given 6 gm. of human plasma fraction I which contained 50 per cent clottable material (obtained from the Institute for Blood Transfusion and Plasma Fractionation, Tel Aviv; amounts of fibrinogen mentioned hereafter and in Figure 1 refer to clottable material). On February 1 the temperature rose to 38°C., numerous splinter hemorrhages appeared under the nails of the first three fingers of both hands and clubbing of the fingers was noted for the first time. A Janeway lesion was found on the sole of the left foot. No erythrocytes were found in the urine. The hemoglobin had dropped to 9.6 gm. per cent. The platelet count was 236,000 per cu. mm. Subacute bacterial endocarditis was suspected and, although repeated blood cultures were negative, treatment with penicillin (3,000,000 units per day) and Achromycin® (1 gm. per day) was instituted. The temperature became normal after five days and splinter hemorrhages did not recur. The patient was given 3 gm. fibrinogen intravenously on February 9. She was discharged on February 13 with a prescription for sigmamycin, 1.5 gm. per day.

On February 20 she was readmitted with bronchopneumonia which abated within a few days. She was again given a fibrinogen infusion (3 gm.) and sigmamycin therapy was continued.

She was readmitted for the third time on April 2 with a temperature of 39°C. and moderate dyspnea. The pulse was regular, 120 per minute. The principal findings were marked clubbing, numerous splinter hemorrhages and enlargement of the spleen to 2 cm. below the costal margin. The neck veins were not swollen. There was no edema of the legs. The lungs were clear. The hemoglobin was 9.5 gm. per cent, the platelet count 190,000 per cu. mm. The serum total proteins were 7.0, albumin 3.0, globulins 4.6 gm. per cent. No red cells were found in the urine. The

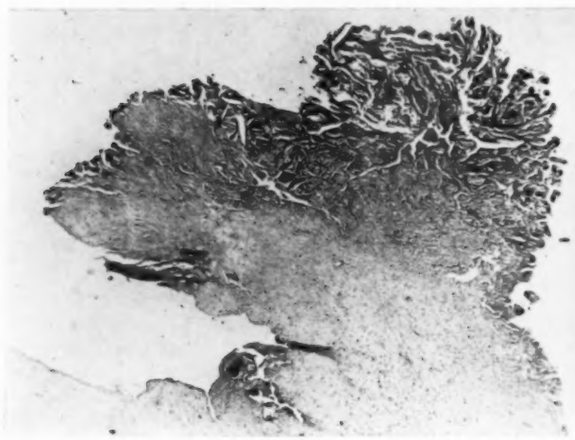

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FIG. 2. Low power view of verrucal vegetation on the atrial surface of the deformed mitral valve. Hematoxylin and eosin.

FIG. 3. Magnification of valvular vegetation in Figure 2 showing fibrinoid material blending imperceptibly with the valvular connective tissue. The darker material (upper part) represents the fibrinoid, containing altered cells with swollen hyperchromatic nuclei. Hematoxylin and eosin, original magnification × 80.

patient was given penicillin intravenously, 20,000,000 units per day. After a few days orthopnea developed and she had severe pain in the right upper portion of the abdomen with increasing enlargement and tenderness of the liver. A pleural effusion appeared on the right side, and the area of heart dullness increased rapidly, reaching the left mid-axillary line and the right mid-clavicular line. On April 20, 160 ml. of blood was removed by pericardial puncture. The patient was treated with repeated fibrinogen infusions (April 21, 29, May 11, 18, 24, 28, June 2, 7, 10) and repeated pericardial taps (on one occasion 750 ml. of blood was removed). A right pleural tap produced 1,500 ml. of bloody serous fluid. She was treated with digitalis, chlorothiazide and mercurial diuretics. The signs of cardiac insufficiency increased, however, and she became refractory to digitalis and diuretics therapy. On June 2, the hemoglobin was 8 gm. per cent, the platelets 250,000 per cu. mm., and the serum total proteins, 7.8, albumin 3.4 and globulin 4.4 gm. per cent.

Whereas the fibrinogen infusions administered during the period from January 20 until June 2 were occasionally followed by a rise in temperature, the fibrinogen infusions administered on June 7 and 10 were followed by a severe chill and profuse sweating. The fibrinogen infusion on June 22 had to be discontinued after twenty minutes when 1.8 gm. of fibrinogen had been administered, because of pallor, sweating, vomiting, a sudden drop in the blood pressure to 40 mm. Hg systolic, and a chill followed by a rise in temperature to 40°C.

The patient's condition deteriorated steadily. She had repeated epistaxis and the hemoglobin dropped to 6 gm. per cent on June 12. On August 5 she was given a blood transfusion, but after 100 ml. was infused, giant urticaria appeared and two hours later she died.

PATHOLOGIC EXAMINATION

At autopsy marked pallor of the mucous membranes was noted. There were no edema, jaundice or cutaneous hemorrhages. Fibrous adhesions partly obliterated the left pleural cavity, which contained 200 ml. of serous fluid; the right pleural cavity contained 1,000 ml. The parietal pleurae were sprinkled with small hemorrhages. The visceral pleurae formed a thick fibrous mantle around the lung parenchyma. There was bilateral severe bronchopneumonia. Two infarctions, one centrally liquefied, were present in the lower lobe of the right lung, they did not appear to be of recent origin. A few medium-sized arteries supplying the infarcted areas were occluded by mural white yellowish thrombotic material. The pericardial cavity, partly obliterated by fibrous adhesions, contained about 100 ml. of serosanguineous fluid. The epicardium was thickened by dense fibrous tissue. The heart weighed 460 gm. and was slightly dilated; the left and right myocardium measured 12 and 4 mm., respectively. The endocardium of the posterior wall of the left atrium above the mitral valve contained a MacCallum patch. The leaflets of the mitral valve were fibrotic, thickened, rigid, shortened and fused at both commissures; the chordae tendineae were also thickened and shortened. Along the line of closure of the mitral valve, lens-sized verrucous vegetations firmly attached to the valvular tissue were found, two on the posterior cusp and one on the anterior cusp; they were light red, nonfriable and of

soft rubbery consistency. The cut surface of the myocardium revealed numerous tiny foci of scarring. In the left ventricle, on the septum, a walnut-sized antemortem blood clot was found.

The peritoneal cavity contained 300 ml. of serous fluid. The mucous membrane of the digestive tract was markedly congested. The liver and spleen were enlarged and congested, and weighed 1,700 and 280 gm., respectively. Apart from some small cortical scars and congestion there were no abnormalities of the kidneys (combined weight 280 gm.). The renal pelvices, the ureters and urinary bladder were normal.

On microscopic examination the mitral leaflets were found to consist of hyalinized fibrous tissue containing many thin-walled blood vessels and they were unevenly infiltrated with lymphocytes, histiocytes and fibroblasts. In a few places palisading histiocytes and fibroblasts, set at right angles to a denuded valvular surface, were observed. The valvular vegetations were made up of smudgy eosinophilic material which blended imperceptibly with the valvular connective tissue and contained, especially at the base, remnants of cells and nuclear debris. (Figs. 2 and 3.) The eosinophilic material showed characteristics of fibrinoid; it was argyrophil, periodic acid-Schiff positive, and contained no fibrin demonstrable with the Weigert's and phosphotungstic acid hematoxylin stains. Apart from these lesions the mitral leaflets showed some "early" changes at their atrial surface, consisting of small irregular subendothelial foci of a smudgy, eosinophilic fibrin-negative and periodic acid-Schiff-positive material. There was no associated inflammatory reaction. Other stages of the same process, probably more advanced, were characterized by superficially located flakes of identical material not covered by endothelium. Supportive evidence for the fibrinoid nature of the eosinophilic material was sought by subjecting the valvular vegetations to digestion by trypsin (fibrinoid is not digested by trypsin whereas fibrin and platelets are [*10–12*]). Serial sections of the mitral leaflets and, for comparison, of a recent subdural hematoma, were cut. The sections were immersed in a 0.1 per cent solution of trypsin in 0.01 M phosphate buffer of pH 7.6 (control in buffer without enzyme) for various periods of time at 37°c. The periodic acid-Schiff and Weigert's fibrin stains were used. The fibrinous meshwork of the subdural hematoma disappeared completely after five hours of tryptic digestion. The controls without enzyme remained unchanged for the whole period of the experiment. The valvular vegetations and flakes remained intact and retained their periodic acid-Schiff positivity up to the termination of the experiment after twenty-four hours of digestion.

The atrial endocardium was somewhat thickened and slightly infiltrated with lymphocytes and mononuclears. It contained a few Aschoff bodies and foci of altered collagen characterized by granularity and increased eosinophilia with or without an associated inflammatory infiltration. There was also slight hyperplasia of the elastic fibers. The intraventricular blood clot consisted of a dense eosinophilic meshwork. In the periphery of the clot fibrinous fibrils could be demonstrated by the Weigert's and phosphotungstic acid hematoxylin stains.

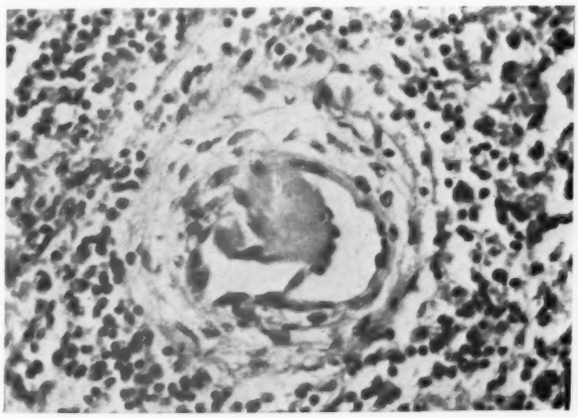

FIG. 4. Spleen. Central artery of lymphatic follicle showing a polypoid structure bulging into the lumen and covered by endothelium. Hematoxylin and eosin, original magnification × 190.

No fibrin could be demonstrated in the exudate in the lung alveoli. The thrombi in the arteries of the lower lobe of the right lung revealed the beginning of peripheral organization, whereas their center was made up of an eosinophilic mass in which only minimal amounts of fibrin, forming a few focal meshworks, could be demonstrated. After four hours of tryptic digestion no residue of the fibrinous meshworks was left.

The liver showed severe chronic congestion with numerous foci of parenchymal hemorrhagic necrosis. There was a slight degree of cardiac fibrosis and marked centrilobular dilatation of the sinusoids with corresponding atrophy of the parenchymal cords. The spleen likewise was chronically congested. Some small to medium-sized arteries in the spleen showed degenerative changes, namely thickening and splitting of the walls, eosinophilic subendothelial hyalinization and partial occlusion of the lumen by a polypoid, eosinophilic, argyrophil, periodic acid-Schiff-positive and fibrin-negative structure, covered by endothelium. (Fig. 4.) The lymph nodes showed reticular hyperplasia, crowding of the sinuses with polymorphonuclear leukocytes and erythrophagocytosis. In the congested kidneys cortical scarring of two types was found: thin, radially arranged, scarred streaks and localized flat subcapsular scars, both presumably related to circulatory disturbances [*13*]. In agreement with this was the finding of a number of small arteries which contained recanalized eosinophilic masses. Occlusion of some small blood vessels by fibrous plugs was observed in the skin.

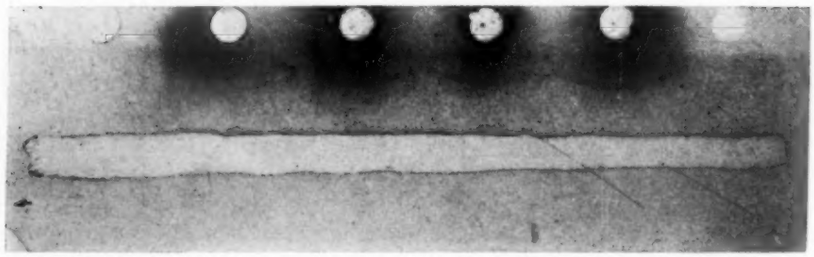

FIG. 5. Precipitation in gel. Purified human fibrinogen, in trough, against patient's serums—white circles. From left to right: February 19, June 7, 9, 22, August 5, postmortem.

ANTIFIBRINOGEN ANTIBODY, DISAPPEARANCE RATE OF INFUSED FIBRINOGEN AND SKIN HYPERSENSITIVITY TO FIBRINOGEN

To determine the frequency of fibrinogen infusion required to maintain a hemostatic plasma fibrinogen level, the plasma fibrinogen disappearance rate was estimated. The rapid disappearance of fibrinogen from the circulation observed after the infusion of June 7 (vide seq.), in conjunction with the severe infusion reaction, led to the search for an antifibrinogen antibody in the patient's serum. Fortunately, a plasma sample obtained on February 19, in the period prior to the severe infusion reactions, was available for comparison.

Precipitin Tests. Precipitin tests were performed using serial twofold plasma dilutions. The antigens were a 0.1 per cent solution of bovine fibrinogen (fibrinogen, Behringwerke Marburg-Lahn, batch 430 A) or plasma Cohn fraction I (the same as used for the infusions) purified according to the method of Laki [*8*] and containing 94 to 95 per cent thrombin-clottable protein. The precipitin reaction was read after two hours' incubation at 37°C. and after twenty-four hours at room temperature. Precipitation in agar gel was performed by the double gel diffusion method of Ouchterlony [*9*], using 1 per cent agar gel in 0.3 M buffered KCl solution, pH 7.4, and a 1 per cent purified fibrinogen solution in the same buffer.

Whereas the results of precipitin tests by the test tube and gel diffusion methods, using both bovine and human fibrinogen antigens, were negative with plasma obtained on February 19, positive reactions were observed with the plasmas of June 7, 9, 22 and August 5, all of which had been obtained preceding the fibrinogen infusions given on those days. Their respective titers were $\frac{1}{8}$, $\frac{1}{32}$, $\frac{1}{32}$, $\frac{1}{16}$. No antibody could be demonstrated in the blood taken one hour after the blood transfusion administered preterminally on August 5 and in the postmortem blood. Figure 5 shows the precipitation lines obtained with the different plasmas collected before and following the appearance of the antibody, using human fibrinogen. The precipitation lines correspond to the test tube precipitin tests in that they are clearly visible at precipitation titers $\frac{1}{16}$ and $\frac{1}{32}$. The reaction to precipitin tests performed with the patient's serums and the supernatants of human and bovine fibrinogen preparations clotted by thrombin was negative.

Rate of Disappearance of Infused Fibrinogen from the Plasma. Plasma fibrinogen was assayed by the method of Ratnoff and Menzie [*7*]. The rates of disappearance of infused fibrinogen from the plasma on four different occasions, two prior to the appearance of antifibrinogen antibody and two when the antibody was present, may be compared in Figure 1. It can be seen that, prior to the appearance of the antibody, fibrinogen could be demonstrated in the plasma by addition of thrombin even twenty days after the infusion of 3 gm. of clottable fibrinogen, whereas following the appearance of the antibody after infusion of the same amount no fibrinogen could be detected after one and a half days. The plasma fibrinogen level observed the day after the infusion, i.e., after about eighteen hours, was much lower after the antibody had appeared than before.

Skin Tests. An intradermal injection given to the patient on June 24 (two days after the severe infusion reaction) of 0.1 ml. of a 0.1 per cent solution of human plasma fraction I in saline solution was followed after ten minutes by erythema, and after two hours by a swelling with a diameter of about 1 cm. The swelling gradually increased, reaching a maximum after eighteen hours and disappeared after three days. A similar skin reaction of lesser intensity was

obtained with 0.1 ml. of a 0.01 per cent solution of human fraction I. A saline solution control in the patient and an intradermal injection of the fibrinogen solutions given to two normal subjects were negative.

A Prausnitz-Küstner test was performed with the patient's antifibrinogen-containing plasma obtained under sterile conditions on July 20 and additionally sterilized by ultraviolet radiation. Following the intradermal injection of 0.1 ml. of patient's plasma given to a normal subject, a local swelling appeared within five minutes followed after thirty minutes by erythema attaining a diameter of 15 mm. after one hour. The reaction disappeared after six hours. After forty-eight hours an injection of 0.1 ml. of the 0.1 per cent human fraction I solution was given to the same areas, but no reaction was observed. Controls with saline solution and plasma from another normal subject were negative.

COMMENTS

In this sixteen year old patient with congenital afibrinogenemia a circulating antifibrinogen antibody was detected after she had received nine infusions of human plasma fraction I and one blood transfusion within a period of four and a half months. That the antibody was specific for fibrinogen and not directed against other antigens, possibly present in the fraction I preparation, follows from its precipitation reaction with purified human fibrinogen, its negative reaction with the supernatant of human fibrinogen clotted by thrombin, its reaction with a purified bovine fibrinogen preparation and, indirectly, from the increased disappearance rate of infused human fibrinogen associated with its presence. Moreover, it would be improbable that the patient, whose only abnormality was the absence of fibrinogen from her plasma, would produce an antibody against other plasma proteins which she herself possessed. Indeed Brönnimann [*4*] observed that serum transfusion was well tolerated in his afibrinogenemic patient in whom an antifibrinogen antibody and hypersensitivity to plasma had developed. The clinical importance of the antifibrinogen antibody lies in its shortening the period of maintenance of a hemostatic fibrinogen level and thus precluding further fibrinogen therapy because of severe infusion reaction.

The increase of the 50 per cent fibrinogen turnover rate in this patient occurring with the appearance of the antibody may be understood in the light of the work of Gitlin et al. [*14*] and Dixon et al. [*15*] in rabbits and of Fletcher et al. [*16*] in man, demonstrating rapid elimination of heterologous protein antigen from the circulation after immunization. Moreover it was shown by Dixon and Talmadge [*17*] that the antigen, once combined with the antibody, was catabolized rapidly. The fibrinogen values determined in our patient by the clotting procedure (which admittedly is of limited accuracy) indicated a plasma half life of infused fibrinogen in the preantibody period (allowing for an initial two days equilibration period [*3*]) of twelve to fourteen days, whereas in the antibody period it was of less than one day's duration.

The long half life of the fibrinogen before the development of the antibody is noteworthy. The data for fibrinogen half life in the literature are conflicting. Madden and Gould [*18*] reported an average fibrinogen half life of 5.6 days in normal human subjects fed S^{35}-labeled methionine, and Gerdes and Maurer [*19*], Gitlin and Borges [*3*], Frick [*2*] and Castex and Pavlovsky [*20*] found fibrinogen half lives of about four days in subjects with congenital afibrinogenemia. Diamond's data [*21*], on the other hand, indicate a half life of about fourteen days. The question may be asked whether these differences in fibrinogen half life are due to different technics of fibrinogen determination or to individual variations (Madden and Gould [*18*] and Volwiler et al. [*22*] found maximum values up to eight days), or whether in some cases the relatively short half lives may have reflected antifibrinogen activity. Indeed, the patients examined for fibrinogen turnover rate by Gitlin and Borges [*3*], Castex and Pavlovsky [*20*] and Frick [*2*] had all been previously transfused with blood, plasma or fibrinogen. It was shown by Dixon et al. [*15*] that the anamnestic antibody response to the intravenous administration of antigen may be associated with decreases in circulating antigen half life of more than 50 per cent. It is clear from our observations (plasma of June 7 and 10) that whereas clottable fibrinogen disappears rapidly from the blood stream in the presence of antifibrinogen antibody, transfusion reactions need not always be so severe as to necessitate interruption of the transfusion. A parallel may be found in patients treated with intravenously administered streptokinase [*16*] in whom rapid inactivation of the infused antigen is not necessarily accompanied by transfusion reaction.

The positive skin reaction of the patient to intradermally injected human plasma fraction I was of the immediate type, presumably reflecting a vascular response to the reaction of the injected fibrinogen with patient's antibody. An attempt to perform a Prausnitz-Küstner reaction by transferring the patient's serum into the skin of a normal subject led again to an immediate skin reaction, this time presumably due to the reaction between the patient's antibody and the normal subject's fibrinogen. It has been demonstrated by Gitlin, Landing and Whipple [*23*] and Gitlin and Borges [*3*] that fibrinogen is present extravascularly in the connective tissue of the skin of normal subjects and of patients with afibrinogenemia who had received an infusion of fibrinogen. The negative reaction to the subsequent injection of fibrinogen into the site of serum transfer may be explained by the binding of all transferred antifibrinogen antibody to the fibrinogen of the normal subject's skin.

The severe shock occurring after the fibrinogen infusion of June 22 was clearly an anaphylactic event due to intravascular fibrinogen-antifibrinogen antibody reaction. The severe giant urticaria following the blood transfusion on August 5 similarly represents an immediate hypersensitivity reaction associated with the circulating antibody [*24*].

Although administration of fibrinogen in the form of blood, plasma or fraction I has been frequently employed in patients with afibrinogenemia there have been only two reports of severe transfusion reaction, one by De Silva and Thanabalasundaram [*25*] and one by Brönnimann [*4*], and antifibrinogen antibody has been demonstrated only once [*4*]. It is possible that the non-occurrence of antifibrinogen antibody in patients with congenital "afibrinogenemia" is due to having minute amounts of fibrinogen in their plasma [*3,26*], and actually being *hypo*fibrinogenemic. Another possible explanation of the different propensity of subjects with congenital afibrinogenemia to produce antifibrinogen antibody may be the development of immune tolerance in some of them, due to placental transfer of fibrinogen from the mother. Non-occurrence of placental fibrinogen passage may then explain the development of antifibrinogen antibody following fibrinogen infusion. Transplacental passage of large molecules, such as albumin [*27*], gamma globulin [*28,29*] and even virus [*30*] and red blood cells [*31*], has been proved. Although we did not find information in the literature on placental fibrinogen transfer, its occurrence seems quite likely in view of the relatively small diameter of the fibrinogen molecule, 65 Å [*32*], and the possible role of pinocytosis in placental transfer of large molecules [*33*].

Of special interest is the occurrence in a patient with congenital afibrinogenemia of a mitral valvular lesion with the appearance of healed organized rheumatic valvular endocarditis. Apparently, the deposit of fibrin on damaged leaflets during the active rheumatic stage is no essential prerequisite for the development of the valvular deformation which, in the present case, may have been due to organization of deposits consisting solely of agglutinated platelets.

Although the presence of Aschoff bodies, the foci of altered collagen and the palisading histiocytes and fibroblasts, set at right angles to the valvular surface, may indicate recent rheumatic activity [*34,35*], the verrucous vegetations on the mitral leaflets were not rheumatic in nature but typical of the lesions described by Allen and Sirota [*36*] as "degenerative verrucal endocardiosis." The combination of peripheral vascular changes, most typical in the spleen, and verrucal endocardiosis is reminiscent of those found in thrombotic thrombocytopenic purpura [*10,37,38*] and considered by various authors [*37,39*] as a reaction of the hypersensitivity type. The vegetations consisted of material having the characteristics of fibrinoid, i.e., smudgy eosinophilic, argyrophil, periodic acid-Schiff-positive, negative for fibrin staining and not digestible by trypsin [*10*]. The nature of fibrinoid is still obscure but there is considerable evidence that it is a precipitate of altered fibrinogen or fibrin [*40*].

Whereas in hypersensitivity reactions [*40*] and in the Shwartzman phenomenon [*41*] the fibrinoid precipitate presumably arises from a normal body constituent—fibrinogen—in the present case of congenital afibrinogenemia, the fibrinoid may represent a precipitate of the infused antigen (fibrinogen) by the antifibrinogen antibody.

SUMMARY

In a sixteen year old girl with congenital afibrinogenemia and rheumatic valvular heart disease an antifibrinogen antibody developed following repeated infusions of human plasma fraction I.

The appearance of the antibody was associated with severe infusion reactions, an increase in plasma fibrinogen disappearance rate and skin hypersensitivity to fibrinogen.

Postmortem examination revealed fibrinoid lesions of the cardiovascular system.

Acknowledgment: We are greatly indebted to Dr. Julian Casper of the Pathology Department for his advice and to Mr. Aureliu Bratu and Mrs. Kay Norton and Mr. Zwi Schleifstein for their technical assistance.

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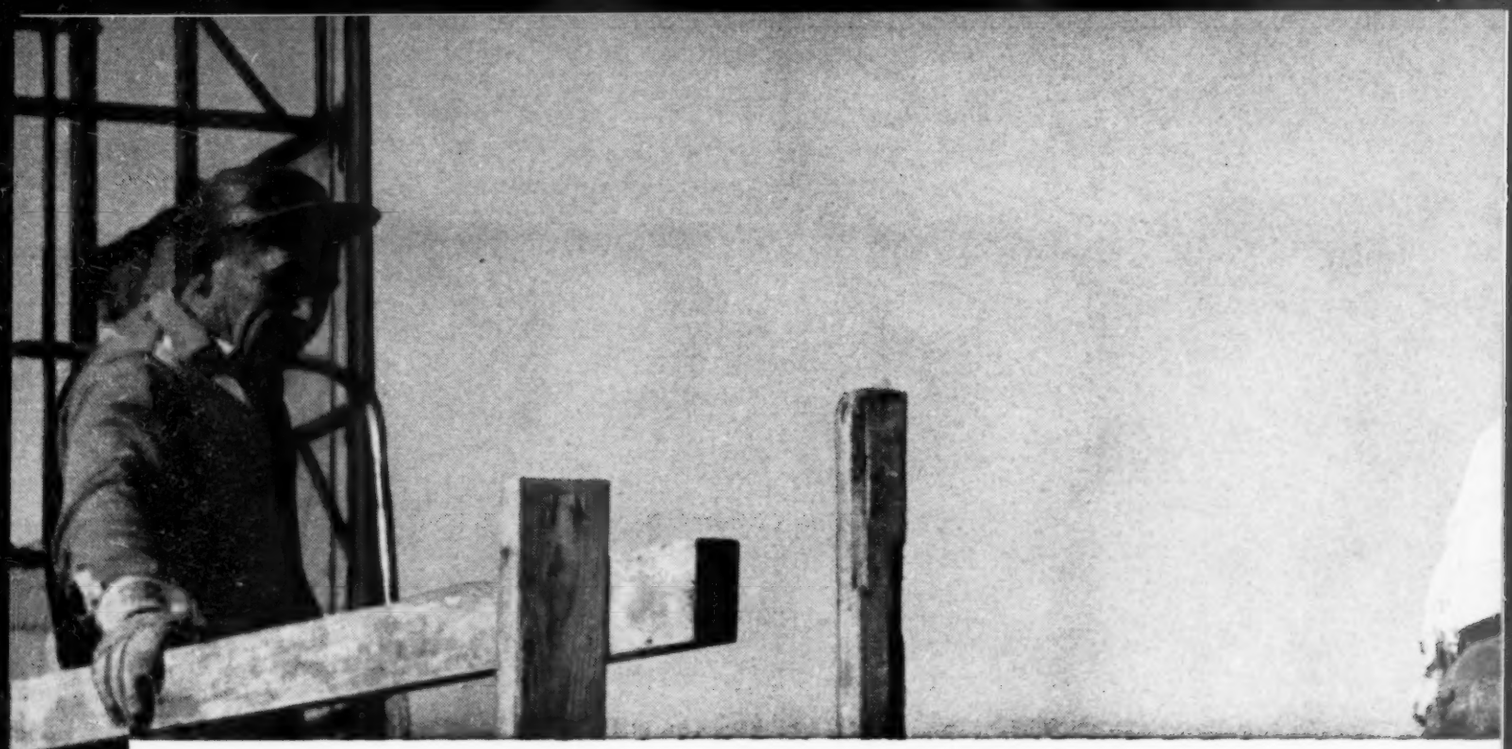

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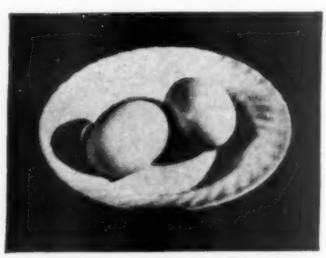

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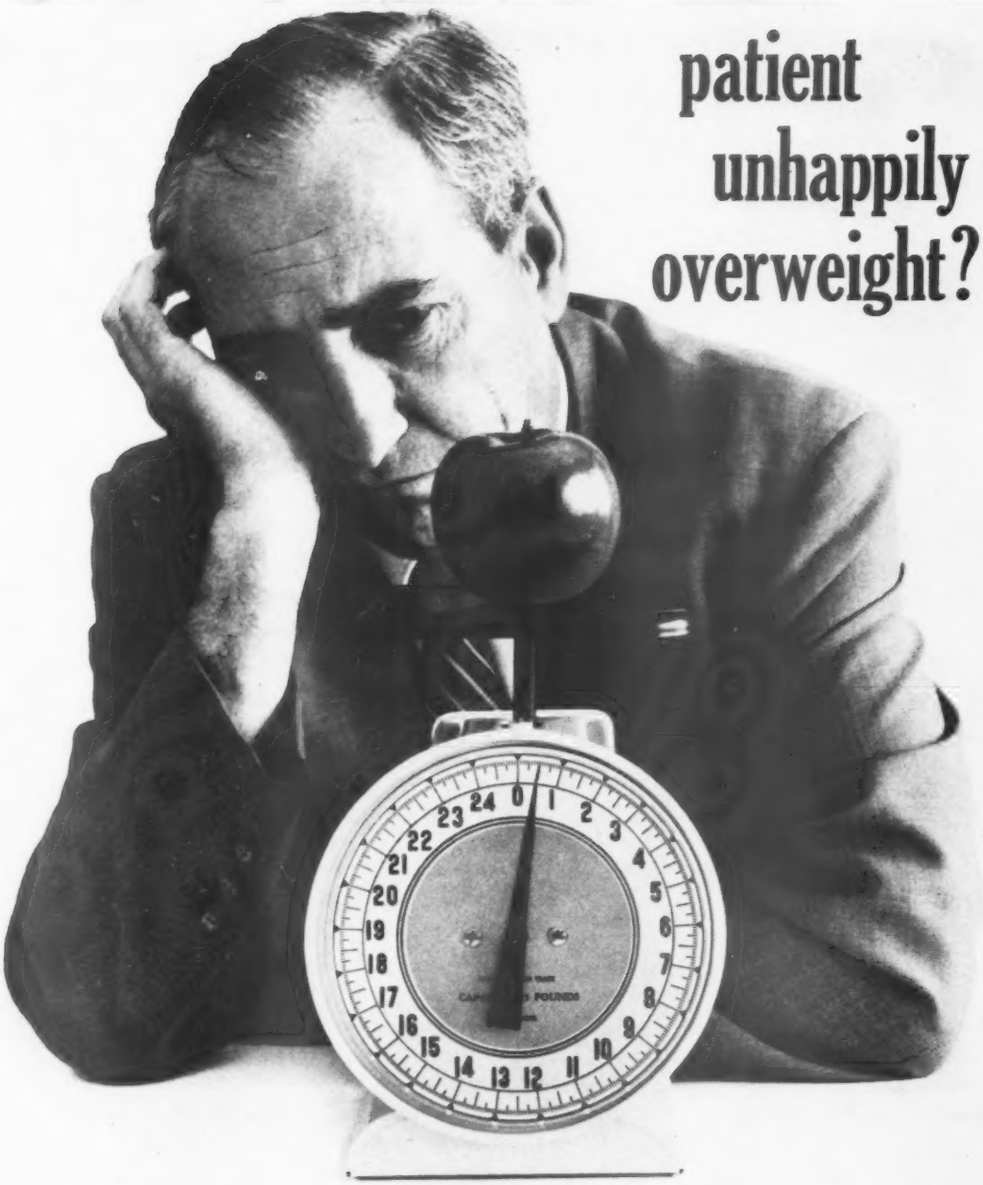

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[1] Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

urge your patients to drink

orange juice

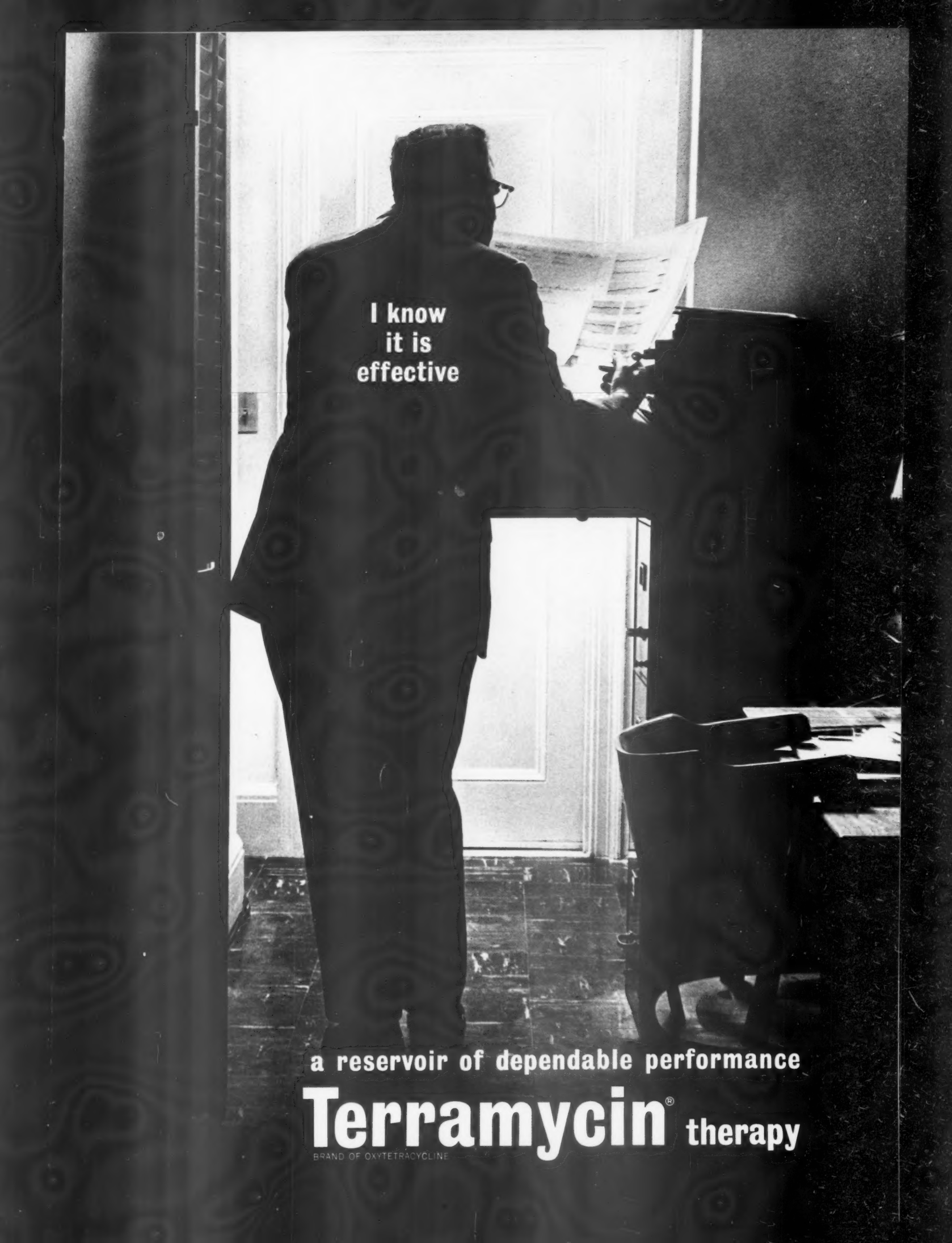
A rich natural source of potassium is important to you and your patients because potassium deficiency has become a serious, recurrent problem in the modern-day treatment of many diseases.

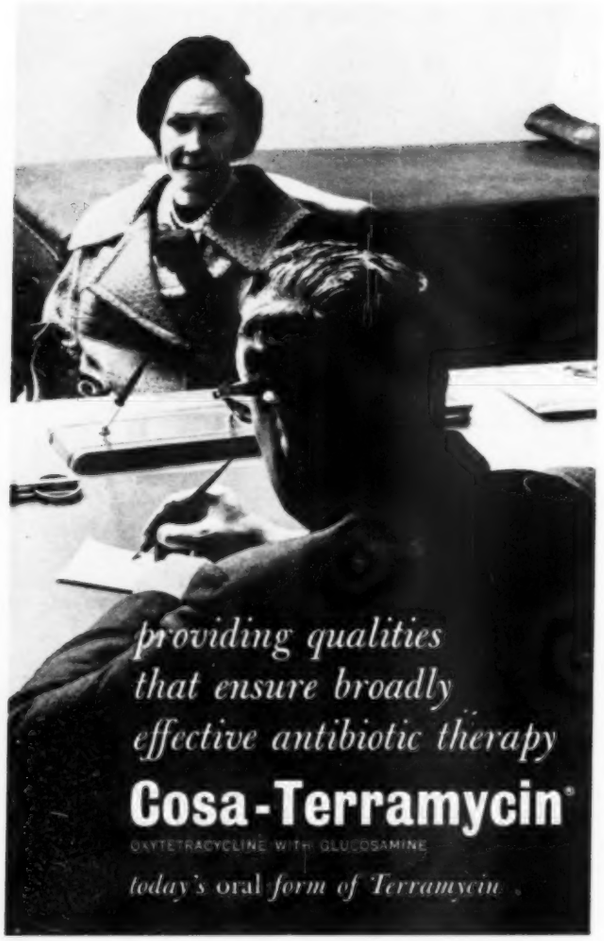
Several valuable new drugs unfortunately drain the body of potassium. Patients receiving these preparations run the danger of a potassium deficiency severe enough to disturb renal function and cause or aggravate edema. Supplementary potassium, therefore, preferably from a rich natural source like Florida orange juice, should always accompany vigorous, prolonged treatment with therapeutic agents of this type.

What better way is there to supply this necessary potassium than for your patient to drink a glass of orange juice each time he takes his medication? . . . What pleasanter source of potassium than delicious, refreshing *Florida orange juice* — either freshly squeezed, frozen, or canned? In any form orange juice is rich in potassium and vitamin C. For the heart failure patient it's important, too, that supplementary potassium tends to reduce the intensity of sodium retention and lessens the threat of edema.

Every 8-ounce glass of Florida orange juice, whether from concentrate or from fresh oranges, contains approximately 446 mg. potassium.

FLORIDA CITRUS COMMISSION, LAKELAND, FLORIDA


I know
it is
effective
a reservoir of dependable performance
Terramycin® therapy
BRAND OF OXYTETRACYCLINE



The continuing clinical effectiveness of Terramycin therapy derives as always from its proven antibiotic characteristics—rapid absorption; notably wide distribution in body tissues and fluids; high, active urinary concentrations; and a broad anti-infective spectrum embracing even such a troublesome organism as Pseudomonas. Additionally, Terramycin therapy provides the assurance of a 10-year record of exceptional toleration.

IN BRIEF

Cosa-Terramycin provides oxytetracycline (Terramycin®) with glucosamine for enhanced absorption.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms), Cosa-Terramycin is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: Adults: 1 Gm. of oxytetracycline daily in four divided doses is usually effective. In *severe* infections, a larger dosage (2-4 Gm. daily) may be indicated. Infants and children: 10-20 mg. of oxytetracycline per lb. of body weight daily. Certain diseases are treated in courses.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms — particularly monilia and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terramycin Capsules,* 250 mg. and 125 mg. Terramycin is also available in: *Cosa-Terrabon® Oral Suspension,* a palatable preconstituted aqueous suspension containing 125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; *Cosa-Terrabon® Pediatric Drops,* a palatable preconstituted aqueous suspension containing 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper; and *Terramycin Intramuscular Solution, conveniently preconstituted,* in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.

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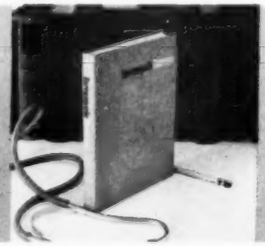

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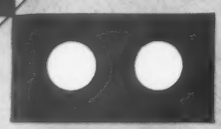
trouble-free
for the
hypertensive patient

RAUWILOID®
alseroxylon, 2 mg.



Just
2 tablets
at bedtime

worry-free
for the
physician

Eight years of continuous use...some 600,000,000 patient-days of effective, safe therapy with RAUWILOID ...prove enduring patient-acceptance and physician-satisfaction...*without any revisions of claims, changes of dosage, or additional side actions encountered.*

RAUWILOID
is an original development of

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Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE®, succinylsulfathiazole—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help provide rapid symptomatic relief.

Additional information on CREMOMYCIN is available to physicians on request.

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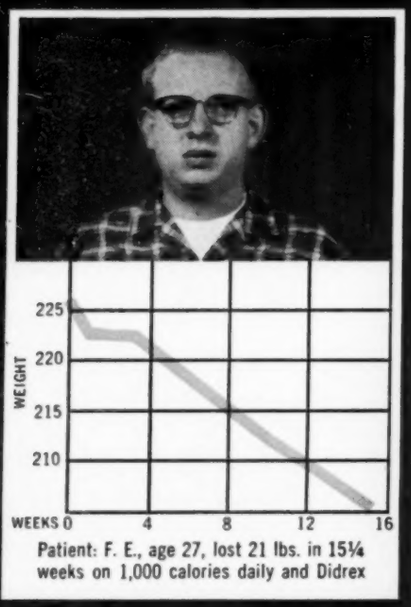
effectively relieves distress of
hot flashes · sweating · headache
· excessive fatigability
· irritability · palpitation · insomnia

"A double blind study shows that the integrative action of... Bellergal Spacetabs is well suited for the symptomatic treatment of patients with vasomotor symptoms. Excellent to good results were achieved in 78 per cent of all complaints in all ambulatory patients treated with Bellergal Spacetabs... Symptoms of autonomic instability in patients with psychosomatic disorders alone, in those in the menopause, or in those in whom it was concomitant with organic disease were well controlled." Bernstein, A. and Simon, F.: Angiology 9:197, August 1958.

BELLERGAL SPACETABS — Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg.
Dosage: 1 in the morning, and 1 in the evening.

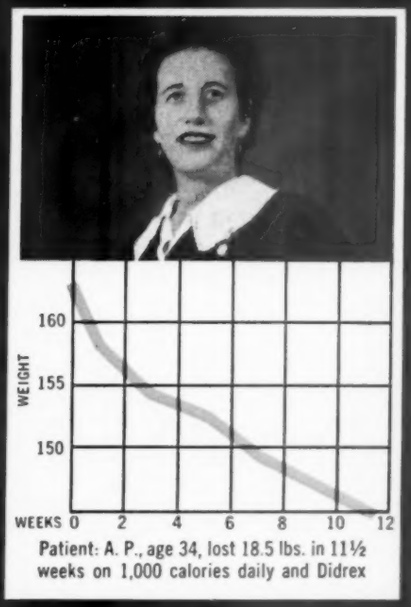
BELLERGAL TABLETS — Bellafoline 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg.
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.

SANDOZ



Patient: F. E., age 27, lost 21 lbs. in 15¼ weeks on 1,000 calories daily and Didrex

Patient: H. H., age 37, lost 14.5 lbs. in 9½ weeks on 1,000 calories daily and Didrex

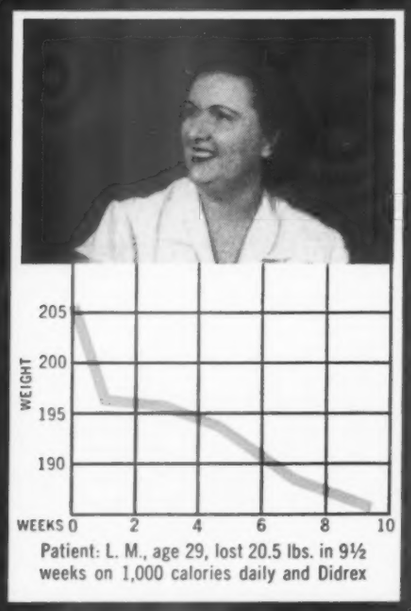


Patient: A. P., age 34, lost 18.5 lbs. in 11½ weeks on 1,000 calories daily and Didrex

UPJOHN ANNOUNCES

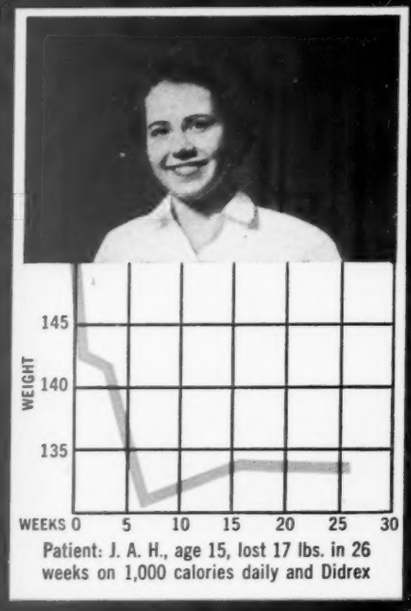
HELPS TAKE WEIGHT OFF PERSISTENTLY

Didrex*



Patient: L. M., age 29, lost 20.5 lbs. in 9½ weeks on 1,000 calories daily and Didrex

Patient: P. M., age 41, lost 10.5 lbs. in 7¼ weeks on 1,000 calories daily and Didrex



Patient: J. A. H., age 15, lost 17 lbs. in 26 weeks on 1,000 calories daily and Didrex

in obesity management

PERSISTENT WEIGHT LOSS WEEK AFTER WEEK

Put it to your patient this way: The basic therapeutic objective of obesity management is to change dietary habits built over months or years of weight accumulation. This takes time and will. Consider Didrex, the new Upjohn appetite suppressant. Happily, it elevates mood which makes dieting more acceptable. More important, it works: "persistent significant weight loss" in patients followed for as long as 20 weeks. Added to your favorite reducing regimen, ½ to 1 Didrex tablet one to three times daily is usually adequate to preclude the "weight plateau" that so often discourages dieters after a few weeks. Available as 50 mg. tablets in bottles of 100. **Upjohn**

The Upjohn Company, Kalamazoo, Michigan

Photos and case histories courtesy Drs. Alan S. Rubenstein, P. V. Dilts and William Conroy, Springfield, Illinois

*Trademark – brand of benzphetamine hydrochloride, UPJOHN

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex®). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex®), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex®). Current Therapeutic Research, 2:33-38 (February) 1960.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N,α-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with ½ or 1 tablet (25 to 50 mg.) in midmorning for several days. Then adjust dosage to suit each patient's need to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., press-coated, scored tablets, in bottles of 100.

for puzzling signs and symptoms...

a reliable diagnostic tool

When signs and symptoms refuse to fall into place, the C.R.P.A. test accurately indicates inflammatory and necrotic diseases. A simple office procedure taking less than two minutes to set up and perform, the C.R.P.A. test can be used *prior to other tests* to determine the necessity for an erythrocyte sedimentation rate or SGO-T level.

Unlike the ESR or SGO-T level, a C.R.P.A. test demonstrates no variability in normal values. It is influenced only by the C-reactive protein in the patient's blood. A positive reaction always indicates pathology;[1] no false positives have ever been reported.

The C.R.P.A. test is a consistently constant indicator of acute myocardial infarction,[1-9] acute rheumatic fever,[10-12] active widespread malignant disease,[1,6,7,12,13] and bacterial infections.[1,5,7,14]

C·R·P·A® *test*

for routine blood chemistry

The reliability of the C.R.P.A. test makes it invaluable in differential diagnoses and routine work-ups. It may be used to deny or confirm ESR and SGO-T readings. Because it is so sensitive it can mark the progress of the disease and measure the effectiveness of therapy.[1,15]

References: 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 3. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:90, 1957. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 5. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 6. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 7. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompuu, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

Complete literature and bibliography available on request.

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ANALGESIC: RELA "...diminished the need for administration of analgesic drugs [aspirin, codeine, meperidine]."[1]

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CLINICAL EFFECTIVENESS: "The effects of carisoprodol [RELA] were shown by relief of pain, and relief of localized muscle spasm...."[1]

RAPID RECOVERY: One fourth the recovery time—RELA treated group of 106 low-back patients averaged 11.5 days—control group, 41 days.[1]

RELA™ RELAXES, EASES ACUTE MUSCLE SPASM & PAIN

CARISOPRODOL

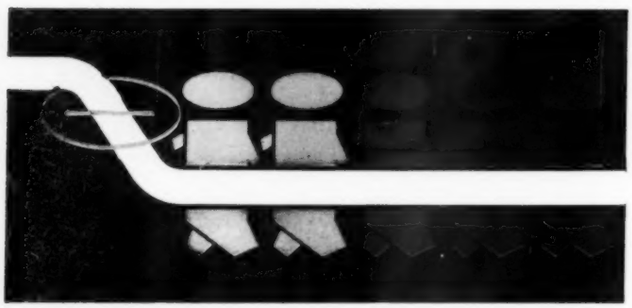
350 mg. TABLETS

Bibliography: 1. Kestler, O. C.: *J.A.M.A.* *171*:2039 (April 30) 1960.

Complete information on RELA including indications, dosage, side effects, and precautions is available to physicians on request.

M-368 JANUARY 1961

HOW CAN THE FULL POTENTIAL OF ORAL THERAPY BE REALIZED?



Diabinese®
BRAND OF CHLORPROPAMIDE

the oral antidiabetic most likely to succeed

The superior effectiveness of chlorpropamide (DIABINESE) is indicated not only by its success in many of the patients in whom tolbutamide has failed,[1] but also by its ability to maintain effective control even when carbohydrate intake is increased because of a more liberal diet.[2] Underscoring this superiority in oral therapy, Hamwi and Skillman[3] observe that in diabetics suitable for sulfonylurea therapy, DIABINESE, "with its more constant blood levels and slower degradation would appear to be the choice in patients predictably less likely to respond because of a clinically more severe state of diabetes."

1. Editorial (A.A.A.) New York J. Med. 59:4130, 1959. 2. Blöch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959. 3. Hamwi, G. J., and Skillman, T. G.: Postgrad. Med. 27:687, 1960.

FOR MAXIMAL ASSURANCE OF CONTINUOUS BLOOD-SUGAR CONTROL WITH ORAL THERAPY—DIABINESE

to realize the full potential of oral therapy

to replace or reduce insulin dosage

to ensure control where diet alone has failed

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.

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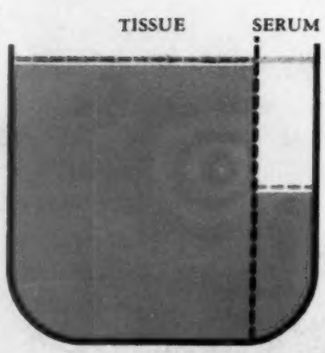
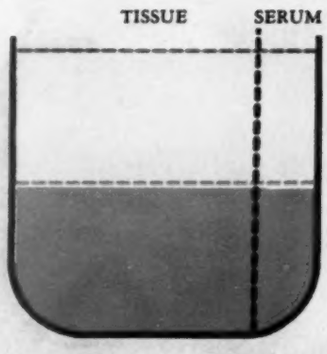
how MER/29 differs from other cholesterol-lowering measures . . .

effect on body pool of cholesterol



OTHER MEASURES

There is no evidence that tissue cholesterol is reduced even in the face of serum cholesterol reduction.



MER/29

Studies in patients have demonstrated a reduction of approximately 40% of *tissue* cholesterol, as well as a significant reduction of the *total* sterol pool.

. . . the first cholesterol-lowering agent to inhibit the formation of cholesterol within the body, reducing both tissue and serum cholesterol

. . . the only specific cholesterol-lowering agent: no demonstrable interference with other vital biochemical processes reported to date; toleration and absence of toxicity established by more than 2 years of clinical investigation

. . . convenient dosage: one 250 mg. capsule daily before breakfast

...and how these differences can benefit your patients

particularly those with high cholesterol levels, coronary artery disease, and generalized atherosclerosis

MER/29 REDUCES CHOLESTEROL IN 8 OUT OF 10 PATIENTS: MER/29 reduces both serum and tissue cholesterol, *irrespective of diet.* Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

CONCURRENT BENEFITS REPORTED IN SOME PATIENTS: In angina patients, some of the concurrent benefits reported include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

DIRECT, SPECIFIC CHOLESTEROL-LOWERING ACTION WITH MER/29: Some agents used to reduce cholesterol have other important primary effects — such as hormonal or vasodilator action. The primary, the *only* known function of MER/29 is to reduce cholesterol.

MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY: Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy. MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include nitroglycerin and PETN, and there have been no reports to date of incompatibility with anticoagulants.

CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver-function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is contraindicated in pregnancy.

SUPPLIED: Bottles of 30 pearl gray capsules.

Complete bibliography and product information available on request.

MER/29

(triparanol)

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The Wm. S. Merrell Company
Division of Richardson-Merrell Inc.
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From the Department of Medicine, Wadsworth Hospital, Veterans Administration Center, Los Angeles, and Department of Medicine and Pathology, University of California Medical Center, Los Angeles, California.

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From the Department of Medicine, Tulare-Kings Counties Hospital, Springville, California.

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From the Departments of Microbioloby and Medicine, the Mount Sinai Hospital, New York, N. Y. These studies were supported in part by research grants from the Squibb Institute for Medical Research and the National Science Foundation.

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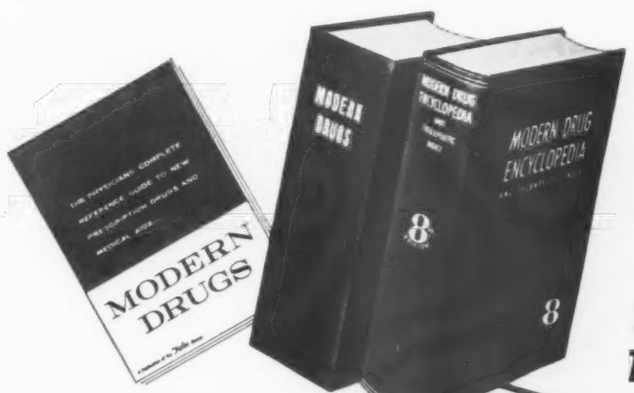

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complication:

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indicated:

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Brief Basic Information

	● Oral Provera*	⟵ I.M. Depo-Provera**
Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only. 50 mg. per cc., in 1 cc. and 5 cc. vials.†

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

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NACTON TABLETS...4 mg.
Average effective dose:
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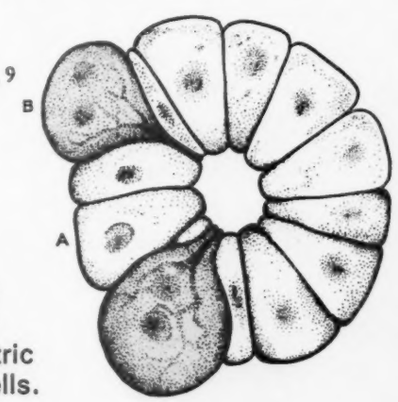

Typical gastric secretory gland.
A—chief cell (pepsin-producing).
B—parietal cell (acid-producing).
NACTON effectively inhibits gastric acid production by the parietal cells.

References:

1. Douthwaite, A. H., and Hunt, J. N.: Effect of "Nacton" in Patients with Duodenal Ulcer, Brit. Med.J. *1*:1030-1034 (May 3) 1958. 2. Douthwaite, A. H.: The Development of the Treatment of Duodenal Ulcer, Proc. Roy. Soc. Med. *51*:1063-1068 (Dec.) 1958. 3. Steigmann, F.: The Problems of Side Effects in Anticholinergic Therapy, to be published. 4. Grossman, M. I., and Tuttle, S. G.: Clinical Report to McNeil Laboratories. 5. Texter, E. C.: Clinical Report to McNeil Laboratories. 6. Cayer, D., and co-workers: Clinical Report to McNeil Laboratories. 7. Lorber, S. H.: Clinical Report to McNeil Laboratories. 8. Walker, G. F.: Therapeutics; Gastric Sedatives, Brit. J. Clin. Pract. *13*:362 (May) 1959. 9. Douthwaite, A. H., Hunt, J. N., and MacDonald, I.: A Long-Acting Inhibitor of Gastric Secretion, Brit. Med. J. *2*:275-276 (Aug. 3) 1957.

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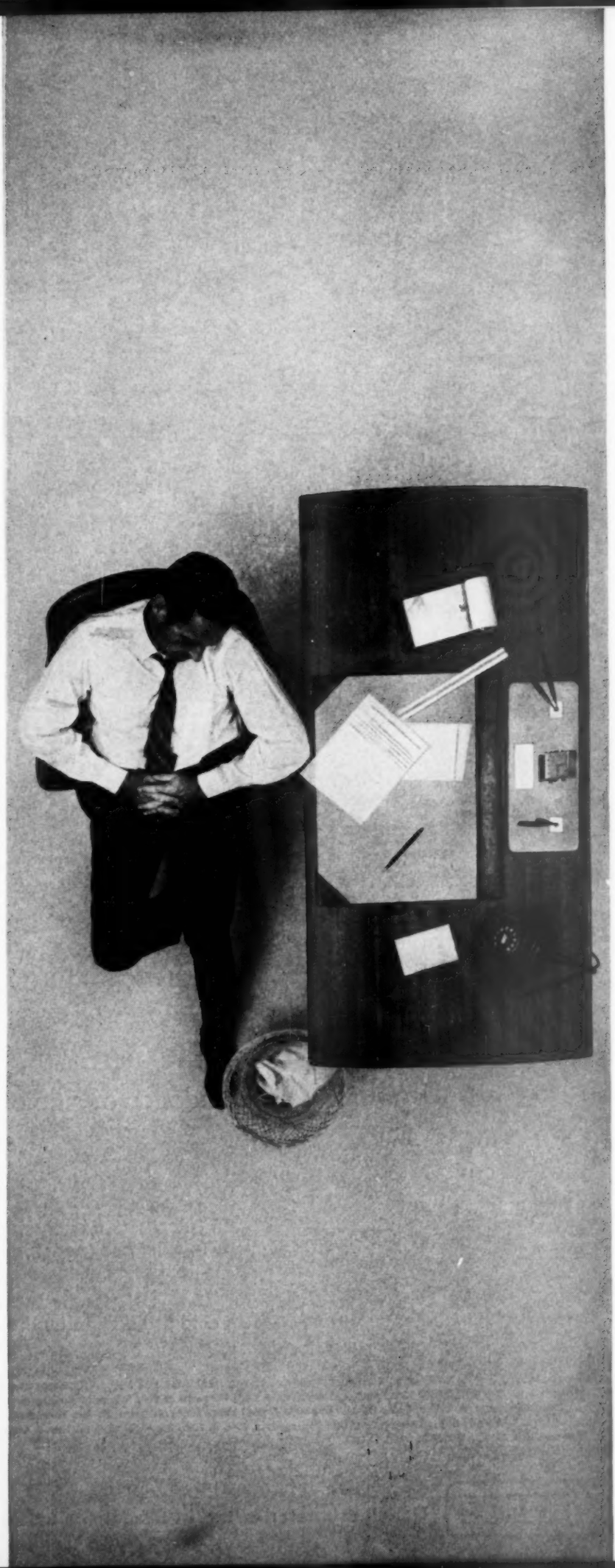

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1. Kasich, A. M., Relief of Nocturnal Pain in Duodenal Ulcer, Am. J. Gastroenterol., 33:66, January, 1960. 2. Kasich, A. M. and Fein, R. D., Hexocyclium Methosulfate in Active Duodenal Ulcer: Evaluation of a New Anticholinergic Drug in Conventional and Long-Acting Forms, Especially its Effect on Gastric pH as studied in 48-hour Analysis, Am. J. Digest. Dis., 3:12, January, 1958. 3. Kasich, A. M., Hexocyclium Methosulfate, a New Anticholinergic Drug in Conventional and Long-Acting Forms: Its Effect on Gastric Secretion, Schweiz. Ztschr. allg. Path., 21:354, 1958.

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Available in 50 mg. tablets. Literature on request. Sold in Canada under the tradename EXNA. 1. Pitts, R. F., Am. J. Med., 24:745, 1958. 2. Ford, R. V., Cur. Ther. Res., 2:51, 1960.

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1. Boyd, S. et al.: A.M.A. 167:704, June 7, 1958.
2. Mason, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar. 1960, p. 13.

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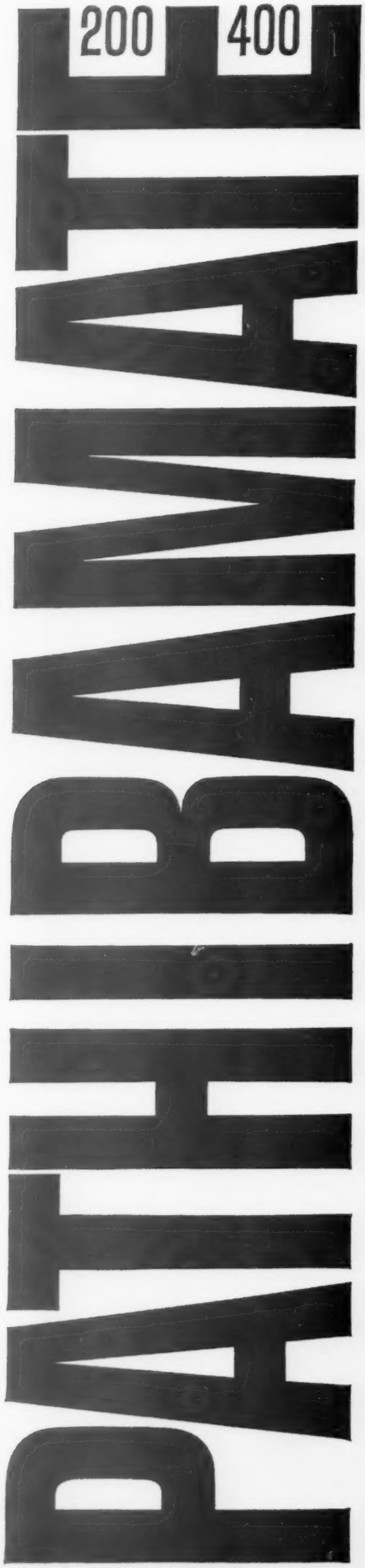

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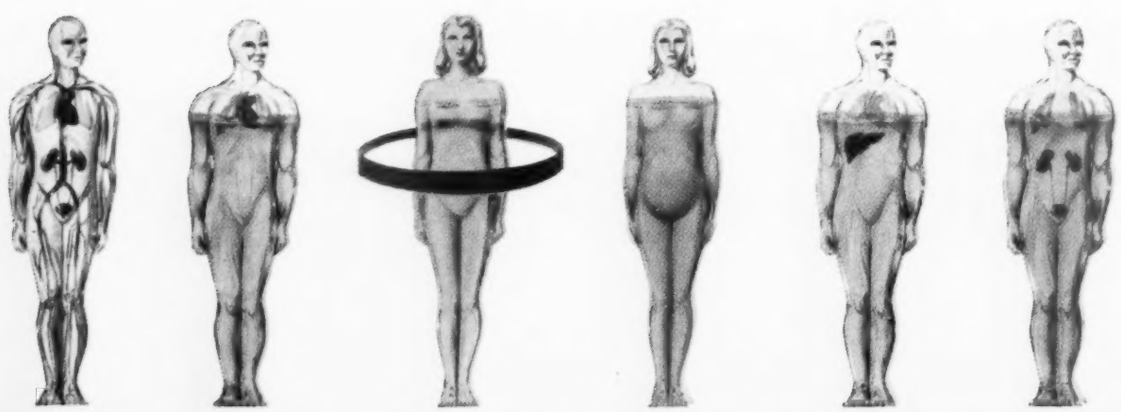

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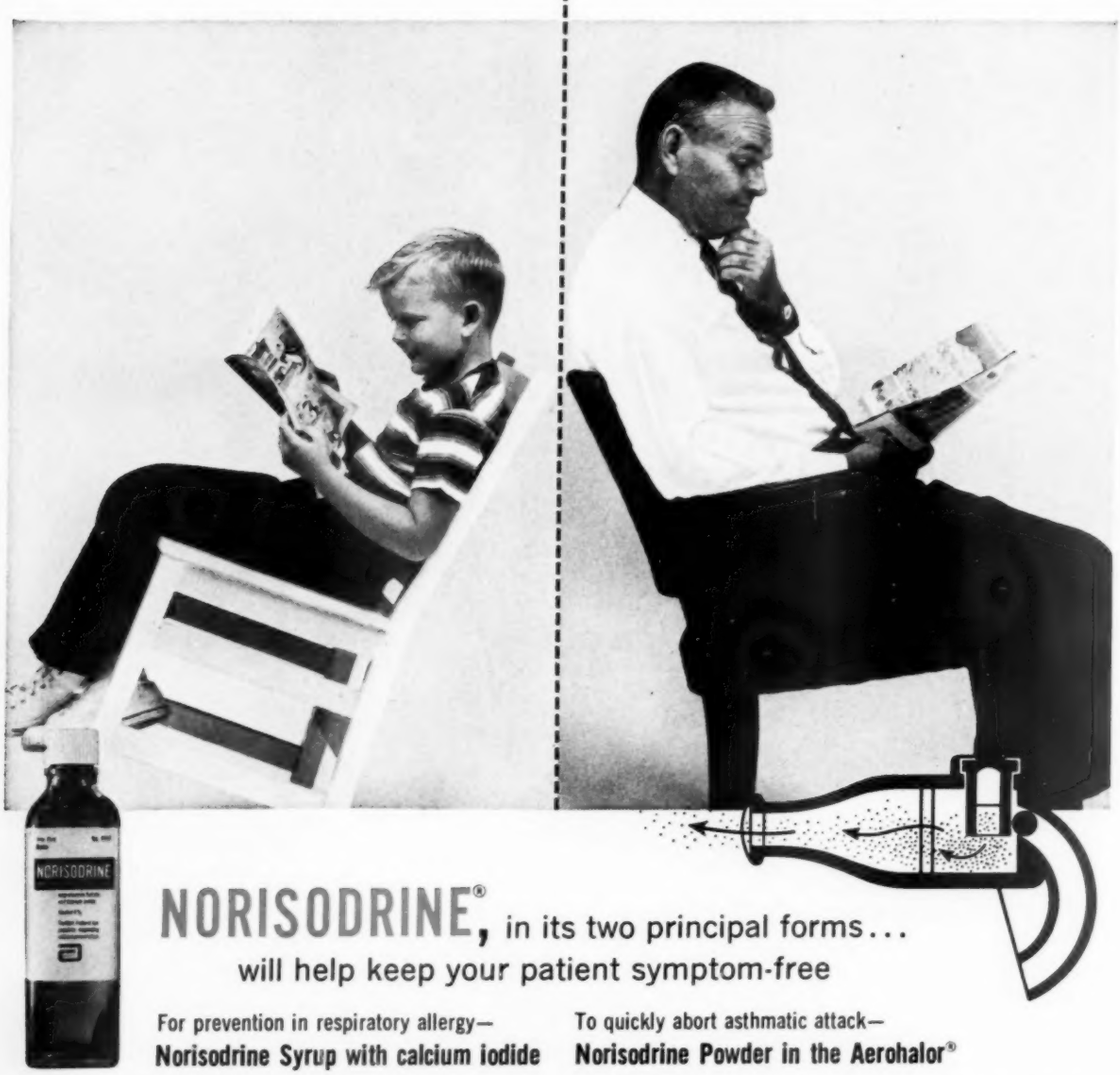

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1. Mellman, E.: Circulation 13:596, 1956.

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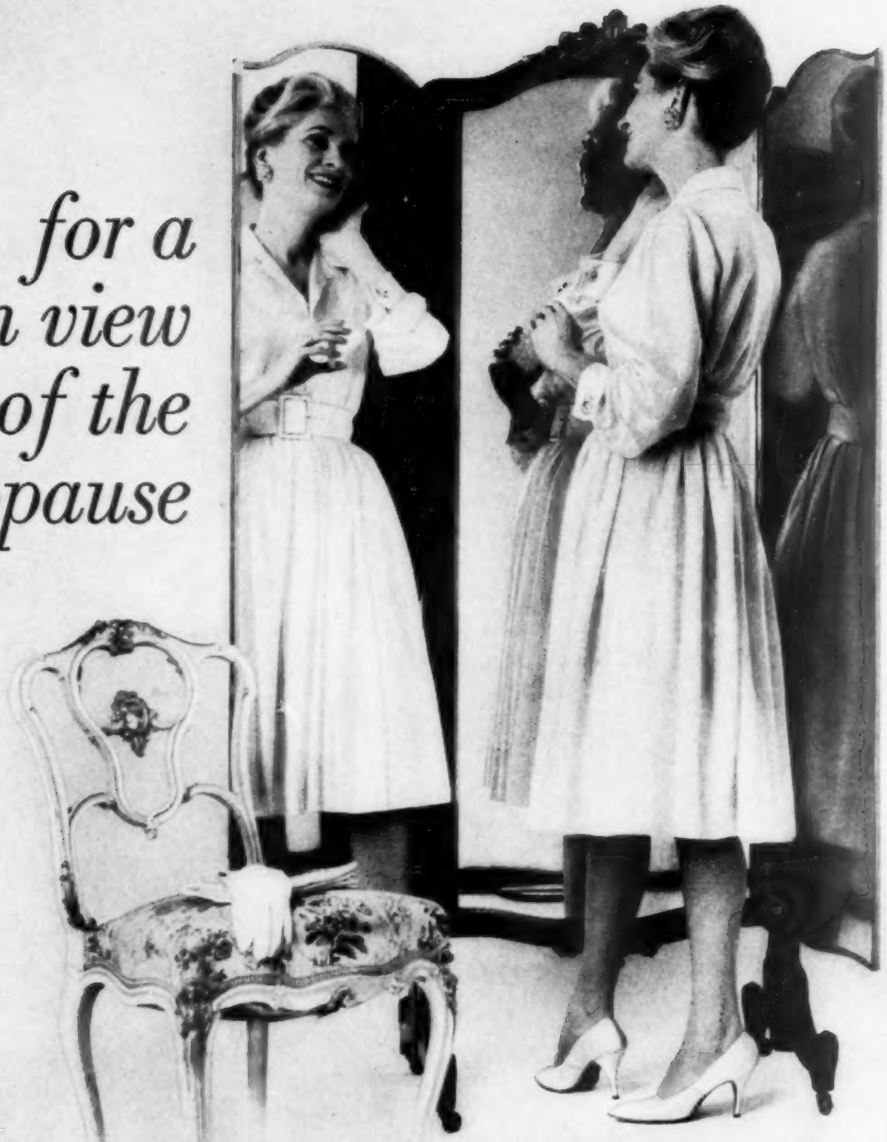

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Supplied: as 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100. Also available as Injection DECADRON Phosphate and new Elixir DECADRON. Additional information on DECADRON is available to physicians on request. DECADRON is a trademark of Merck & Co., Inc.

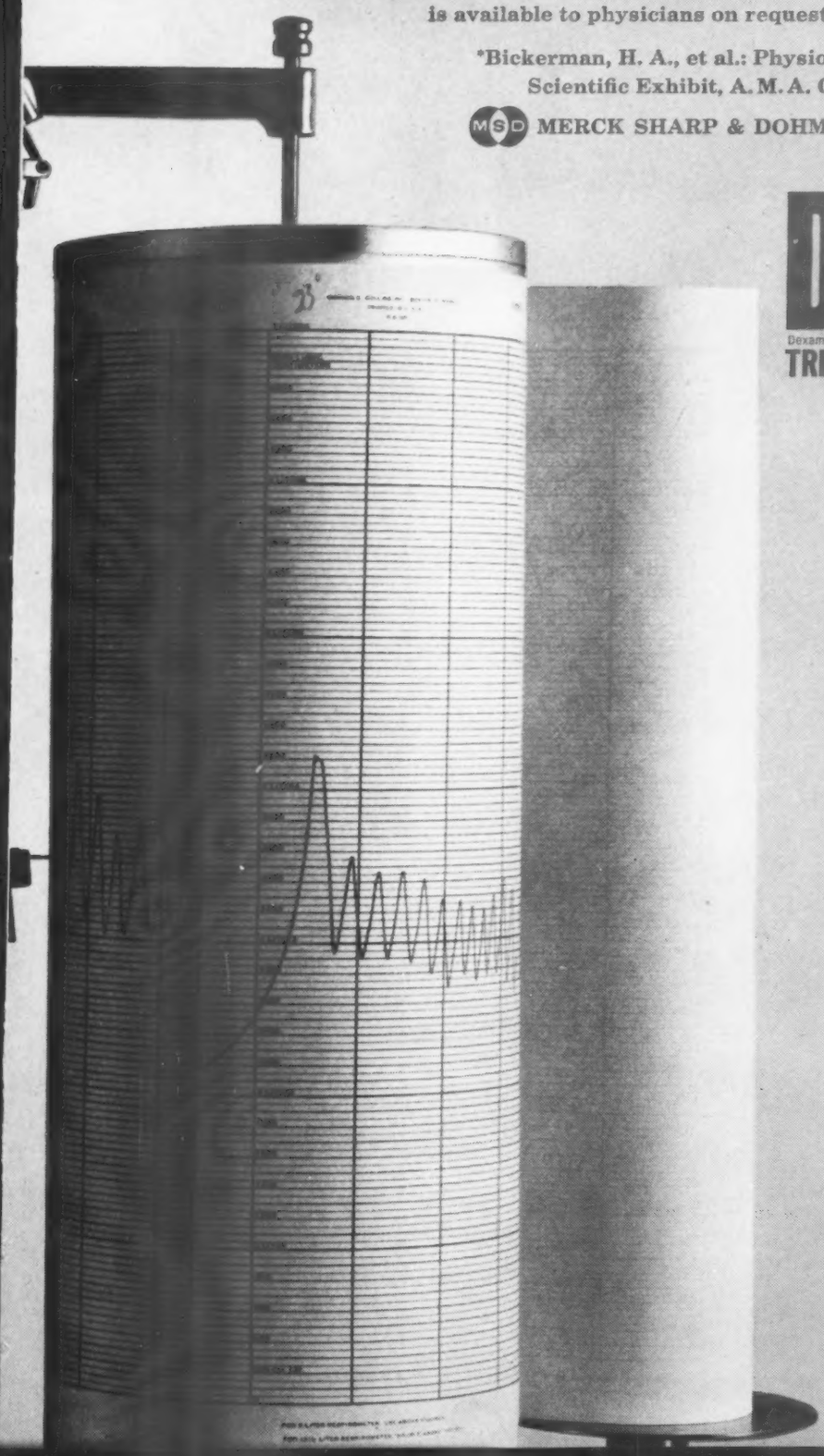
*Bickerman, H. A., et al.: Physiologic and steroid therapy in respiratory disease, Scientific Exhibit, A.M.A. Convention, Atlantic City, N. J., June 8-12, 1959.

MSD MERCK SHARP & DOHME Division of Merck & Co., INC., West Point, Pa.

Decadron®

Dexamethasone

TREATS MORE PATIENTS MORE EFFECTIVELY



You see an improvement within a few days
Thanks to your prompt treatment and the smooth action of Deprol, her depression is relieved and her anxiety and tension calmed – *often in a few days.* She eats well, sleeps well and soon returns to her normal activities.

Lifts depression...as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety...rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety – both at the same time.

Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function – frequently reported with other antidepressant drugs.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate. **Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲®

WALLACE LABORATORIES/*Cranbury, N. J.*

69-2125

Sleep is sorcery...enchanted healer of care. And non-barbiturate Placidyl is the wand that subtly summons it. Placidyl casts a spell both prompt and effective...then lifts it, without hangover, on a refreshed new morning. No magic required to grant slumber to the restive. Just...*sssh!*...Placidyl.

ABBOTT

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Placidyl® (ETHCHLORVYNOL, ABBOTT) **nudges your patient to sleep**

ABBOTT

Geriactive with Filmtab® Gerilets®

Leisuretime, of course, needn't mean a hyper-abundance of activity. However, whatever the interests of your geriatric patient, you'll naturally do everything you can to help make his existence more meaningful.

And, in prescribing Filmtab Gerilets, you're giving the older patient the kind of dietary and therapeutic support which often may contribute to a more productive life.

In checking into Gerilets' comprehensive formula, you'd find these components featured:
B-Complex and Oil-Soluble Vitamins . . . Hematopoietic Factors . . . Lipotropic Factors . . . Hormones . . . Anti-Depressant and Capillary Stability Factors.
An added advantage, appreciated in particular by the finicky patient, is Gerilets' exclusive Filmtab coating. Makes for a streamlined tablet. Also makes it that much easier to stay "Geriactive with Gerilets."

STREAMLINED INTO THE SMALLEST TABLET OF ITS KIND

®FILMTAB—FILM-SEALED TABLETS, ABBOTT; U. S. PAT. NO. 2,881,085. ®GERILETS—GERIATRIC SUPPORTIVE FORMULA, ABBOTT.

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Bedtime dose usually carries the child

cough-free through the night

NON-NARCOTIC

ULO®

Chlophedianol HCl

SYRUP

cough suppressant action	equal to	narcotics
duration of action	greater than	narcotics
side actions	less than	narcotics

compatible with all other indicated medications

Indications: Upper respiratory infections • Common cold • Influenza • Pneumonia • Bronchitis • Tracheitis • Laryngitis • Croup • Pertussis • Pleurisy

There are no known contraindications. Side effects occur only occasionally and are mild. Nausea and dizziness have occurred infrequently; vomiting and drowsiness rarely.

Dosage: Adults: One teaspoonful (25 mg.) 3 or 4 times daily as required.

Children: 6 to 12 years of age, ½ to one teaspoonful (12.5 to 25 mg.) 3 or 4 times daily as required.

2 to 6 years of age, ½ teaspoonful (12.5 mg.) 3 or 4 times daily as required..

Availability: ULO Syrup, 25 mg. per 5 cc. (teaspoonful), in bottles of 12 fluid ounces.

Riker

Northridge, California

Everyday practice report:

Following initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 4026 cases have now been analyzed. In 2260 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

FORHISTAL® maleate (dimethpyrindene maleate CIBA)
LONTABS® (long-acting tablets CIBA)

new Forhistal® rated better than previous therapy in 7 cases out of 10

CIBA
SUMMIT, NEW JERSEY

2/29:OMK